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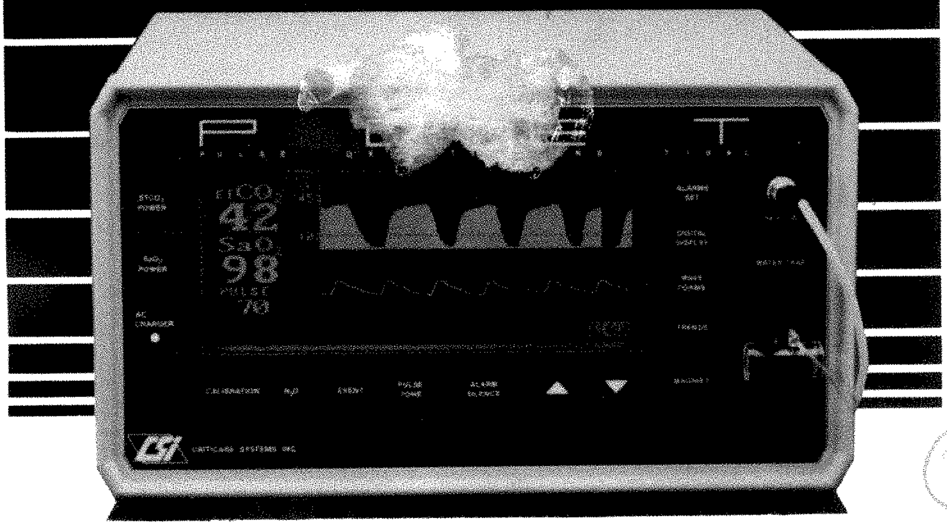

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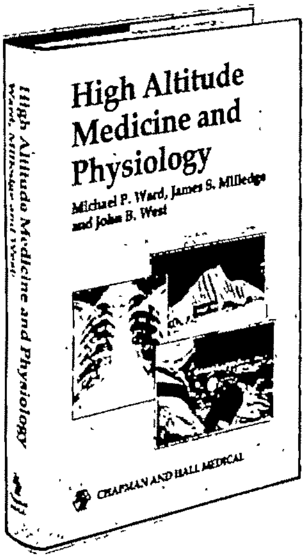

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Der Anaesthesist · 38. Band · Heft 5 · 1989 · S. 225–272 Regional-Anaesthesie · 12. Band · Heft 3 · 1989 · S. 41–62

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Springer-Verlag

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Gedruckt auf säurefreiem Papier

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 63, No.1 JULY 1989

EDITORIAL I

THE PRIMING PRINCIPLE: HOW DOES IT WORK AND SHOULD WE BE USING IT?

The first reports that the onset of neuromuscular block could be hastened by administering non-depolarizing blocking drugs in divided doses (using a small initial dose) appeared in this Journal in 1983 [1, 2]. The small initial dose was subsequently termed the "priming dose" by Foldes [3], and the literature on the "priming principle" increased rapidly. From a clinical standpoint, the use of the priming principle promised the much needed ability to perform tracheal intubation rapidly (60–90 s) using non-depolarizing neuromuscular blocking drugs, a property of particular value in circumstances in which suxamethonium administration is contraindicated. From an "academic" standpoint the almost limitless permutations available by varying the size and proportions of priming and intubating doses, the time interval separating them and the specific agent used, promised a large number of "me too" publications.

The main questions arise when summarizing and critically reviewing the extensive literature on priming, including the communication by Pollard which appears in this issue of the Journal [4], and that of Storella and his colleagues which appeared in the May issue of the Journal [5]. First, does the administration of a non-depolarizing neuromuscular blocker in divided doses significantly hasten the onset of neuromuscular block (and if so, why)? Second, if priming does hasten paralysis, can the principle be used to define the optimum combinations of doses and intervals in order that tracheal intubation may be achieved as safely after non-depolarizing drugs as after suxamethonium (and, used in this way, does the method have any complications or untoward side-effects)? The literature on priming is now sufficiently comprehensive for these questions to be answered with confidence.

The varying conclusions of the published reports on whether or not priming really does shorten the onset of paralysis arise from differences in both the size and proportions of priming and principal dose and the interval separating them. (The confusion has been compounded to some extent by different authors basing their conclusions on different methods of monitoring paralysis, such as the use of single twitch or train-of-four patterns of nerve stimulation, in addition to use of electro- or mechanomyographic methods of response recording.) For example, using atracurium in a priming dose of 50 $\mu g\ kg^{-1}$, an interval of approximately 4–5 min and an intubating dose of 350 $\mu g\ kg^{-1}$, Ramsey and colleagues [6] reported that priming had no effect in hastening onset of block compared with a single bolus dose of 400 $\mu g\ kg^{-1}$ (time to peak effect 165 s primed, 138 s bolus). However, Naguib and colleagues [7] administered a slightly greater total dose of atracurium, either 500 $\mu g\ kg^{-1}$ as a bolus or 60 $\mu g\ kg^{-1}$ as a prime and 440 $\mu g\ kg^{-1}$ 3 min later, and reported peak onset time reduced from 137 to 76.5 s. The precise doses used and the time interval separating them are obviously of crucial importance. In particular, it would appear that the priming dose should be a certain minimum amount for clinically significant differences to be observed. If these minimum requirements are fulfilled, there is no doubt that administering neuromuscular blocking drugs in divided doses does measurably hasten the onset of paralysis. This observation has been documented reliably with all available blocking drugs, although by its very nature the technique is most suited to shorter acting agents, such as vecuronium and atracurium, and the literature on these agents is most comprehensive.

What, then, is the mechanism underlying the phenomenon? Of the theoretical mechanisms which could be evoked, two principal ones emerge for which there is some supporting evidence. First, the priming dose occupies a proportion of (presumably) postsynaptic nicotinic receptors, hence reducing the safety margin present normally in neuromuscular transmission. The intubating dose thus blocks more rapidly that critical mass of receptors necessary for clinical paralysis to occur. In this postsynaptic theory, the priming dose may be thought of as taking up some of the slack which provides the normal safety margin in transmission and it follows that the size of the priming dose is of fundamental importance (in order to occupy a critical mass of receptors), as is the time separating priming and intubating doses (in order to maximize receptor occupancy). The second theory is that the priming dose blocks presynaptic nicotinic receptors, reducing the mobilization and release of acetylcholine such that the intubating dose produces paralysis more rapidly. In the May issue of this journal Storella and co-workers [5] reported their results using an isolated *in vitro* nerve–muscle preparation (which is free from a number of complicating pharmacodynamic influences present in the intact animal such as protein binding, metabolism and excretion) and, using an acceptable mathematical model, compared predicted and measured onset times in both primed and non-primed conditions. They demonstrated clearly that the effectiveness of priming is related to the concentration of drug achieved at the neuromuscular junction at the end of the priming interval; that, using Fick's law of diffusion, the onset of block could be predicted accurately; and that this does not differ in the primed compared with the unprimed state. In addition, Naguib and co-workers [7] have reported previously that different train-of-four ratios present at the end of the priming period are associated with virtually identical onset times after administration of the intubating dose. Taken together, and assuming train-of-four fade reflects some aspect of a presynaptic action of neuromuscular blockers, the reports of Storella and Naguib suggest that presynaptic theories do not have to be evoked in order to explain the mechanism(s) underlying priming. However, it should be noted that both reports use surrogate techniques to infer drug site of action, and more precise methods, such as intracellular recordings and the measurement of miniature end-plate potentials, will be needed before a more definitive conclusion can be reached.

Thus priming works, and does so by reducing the margin of safety present in transmission; but what is the optimum technique and does this provide intubating conditions comparable to those of suxamethonium? It has already been stated that the effectiveness of priming relates directly to the concentration of drug present at the neuromuscular junction at the end of the priming period [5]. This factor is put into clinical context by the observation of two other studies: Baumgarten and colleagues [8] in a series of controlled, randomized, double-blind investigations, used a variety of drugs and dose time intervals and concluded that priming did produce significantly improved intubating conditions compared with an equivalent bolus dose, but that these did not match the uniformly good conditions produced by suxamethonium; similarly, Harropp-Griffiths, Grounds and Moore [9] studied intubating conditions following priming with alcuronium and used a logistic transformation technique to calculate the priming dose needed to produce adequate intubating conditions in 99% of patients at 60 s. This was 106.50 μg kg^{-1}; however, 30% of patients complained of unpleasant side-effects using a dose less than half of this (50 μg kg^{-1}). Thus, at best, priming produces intubating conditions less uniformly acceptable than those provided with suxamethonium, but the priming dose needed for even this limited improvement, compared with a single bolus dose, is associated with an unacceptably high frequency of unpleasant side effects. Storella and colleagues [5] also emphasized that adjustments to priming dose and interval cannot substantially reduce the weakness associated with priming without also slowing the onset of full paralysis. Other authors [6] have been unable to demonstrate any advantage with priming; however, they used a dose which was calculated not to cause an unacceptably high frequency of paralysis, and in these circumstances they were unable to demonstrate any hastening of onset of block.

In an attempt to refine the principle, in order to reduce the incidence of side effects whilst retaining effectiveness, two modifications of the technique have been proposed. One of these is based on the observation that certain combinations of myoneural blockers exhibit synergism [10]; that is, their combined effect is more than the sum of their individual effects. In this issue of the Journal, Pollard [4] has compared alcuronium and tubocurarine—a combination known to exhibit marked synergism—and used them both to prime themselves and to prime each other. He used an ED$_{95}$ dose of each agent, a priming interval of 3 min, and a priming dose of 10% of the principal dose. Control (unprimed) groups were included and he demonstrated that, although priming produced results significantly different from the controls, the use of synergistic pairs as priming and principal drug had only a small effect, which did not reach statistical significance. Thus any advantage which may be present from the use of synergistic combinations of neuromuscular blocking drugs is minor. Donati and colleagues have reported similar results [11] using the synergistic combination of pancuronium and tubocurarine. Both Pollard and Donati concluded that the use of synergistic mixtures may produce some improvement compared with single drug priming; however, this improvement is too small to be of clinical significance.

The other modification suggested is that of sensitivity-adjusted priming [12]. Some preliminary work has been performed in cats in which incremental doses of blocking drugs were used in order to determine the individual dose–response curves of the animals. The authors went on to demonstrate that, using $2 \times ED_{95}$ doses of vecuronium, given as 20 % priming and 80 % principal dose (4-min interval), sensitivity adjusted priming was more reliable than "average dose" priming. This approach—in which individual dose–response relationships have to be determined—is the only proven method of reducing the chances of over priming (sensitive individuals) or under priming (resistant individuals). It is obviously incompatible with most clinical situations and could not be used in precisely those circumstances in which rapid tracheal intubation is required.

Finally, reports of a histaminoid reaction to a priming dose of vecuronium [13] and of pulmonary aspiration following priming with this drug [14] only serve to emphasize the dangers inherent in the technique.

In conclusion, the administration of non-depolarizing neuromuscular blocking drugs in divided doses does hasten the onset of paralysis, although the priming dose needed to provide intubating conditions approaching those of suxamethonium is associated with an unacceptably high incidence of unpleasant and potentially dangerous side effects. Pollard, amongst others, has demonstrated that, although certain techniques may be used to refine and optimize the principle, these either lead to little or no significant improvement in clinical acceptability, or are practically unworkable. The report of Storella and colleagues suggests a kinetic basis for this interesting pharmacological phenomenon which has, however, no useful role in clinical anaesthesia.

R. M. Jones

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EDITORIAL II

VOLATILE ANAESTHETIC AGENTS IN NEUROSURGERY

The effects of anaesthetic agents on the brain and its blood vessels have been well defined. This has allowed rational decisions to be made on the choice of anaesthetic agents for intracranial surgery and has allowed the role of volatile agents to be defined more clearly. This is important particularly when intracranial compliance is reduced, for example by a cerebral tumour or following a head injury, where the administration of volatile anaesthetic agents may cause critical swelling and congestion of the brain.

Anaesthetic agents influence intracranial pressure (ICP) mainly via effects on vessel calibre, either directly or indirectly by depressing ventilation and increasing arterial carbon dioxide tension (Pa_{CO_2}). A change in vessel calibre causes a change in cerebral blood volume (CBV) which alters the volume of the cranial contents and thus ICP. Cerebrovascular autoregulation normally protects the brain from the detrimental effects of changes in arterial pressure, and a deliberate reduction of Pa_{CO_2} is used to reduce vessel calibre and thus reduce brain bulk, so that it is desirable for anaesthetic agents to have little or no effect on cerebral autoregulation or on the carbon dioxide reactivity of the cerebral vessels.

The neuroanaesthetist maintains a constant cerebral perfusion pressure (CPP) during intracranial surgery by avoiding a marked reduction in mean arterial pressure (MAP) or an increase in ICP. Marked surges in arterial pressure must be prevented because these may temporarily overcome normal cerebrovascular autoregulation and the increased pressure in the cerebral capillary bed may initiate or increase cerebral oedema.

Anaesthetic agents may also alter ICP by changing the rate of production or absorption of cerebrospinal fluid (CSF). Enflurane increases the rate of production of CSF and both enflurane and halothane decrease its absorption, whereas isoflurane has no effect on the rate of production or absorption of CSF [1].

A high ICP may have detrimental effects on the brain by reducing CPP and causing cerebral ischaemia, or by causing brain shift through the foramen magnum, tentorium cerebelli or across the midline. When the dura is opened, ICP decreases to zero so that CPP then depends only on MAP, but herniation of the brain through the craniotomy defect occurs if ICP is high at the time the dura is opened. A moderate increase in brain bulk, and thus ICP, leads to increased pressure under the brain retractor, thereby hindering the surgeon and increasing brain trauma. Therefore, during anaesthesia for craniotomy, the anaesthetist minimizes changes in brain bulk and ICP by reducing Pa_{CO_2}, avoiding increase in CVP (e.g. by preventing the patient from coughing and straining), controlling arterial pressure and choosing appropriate anaesthetic agents. The surgeon may require a reduced arterial pressure at certain stages of the operation and, under these circumstances, a degree of cerebral protection against ischaemia is desirable. Anaesthetic agents which reduce cerebral metabolic rate ($CMRo_2$) may be beneficial by providing some cerebral protection against ischaemia. Convulsions, which increase $CMRo_2$ and cause imbalance between cerebral oxygen supply and demand resulting in cerebral hypoxia, are detrimental.

Anaesthetic concentrations of all volatile agents have been shown to increase cerebral blood flow (CBF) and ICP and reduce $CMRo_2$. The changes in ICP are generally greater in those with an increased ICP than in normal patients [2,3]. They also reduce CPP because MAP is decreased and ICP is increased. Of the volatile agents, halothane causes the greatest increase in CBF and ICP and, although it reduces $CMRo_2$, this does not appear to offer any cerebral protection. Marked increases in ICP in patients with increased ICP can be prevented by hyperventilation for at least 10 min before halothane is introduced [4], but even this may not be successful if ICP is increased considerably [2,3]. The majority of investigations show that enflurane has less effect on CBF and ICP than halothane and the largest reported increases in ICP with enflurane are significantly smaller than those reported with halothane [5].

Isoflurane in inspired concentrations of 0.6–1.1

MAC does not alter CBF in man, but 1.6 MAC isoflurane doubles CBF [6] (in contrast, 1.6 MAC halothane trebles CBF). Animal work has shown that isoflurane may enhance the carbon dioxide reactivity of the cerebral vessels [7] and that cerebral autoregulation is impaired significantly only by concentrations greater than 1 MAC [8]. $CMRo_2$ is depressed to a greater extent with isoflurane than with halothane [9] and progressive metabolic depression occurs with concentrations of isoflurane greater than 1 MAC until the electroencephalogram (EEG) becomes isoelectric at approximately 2.5 MAC [10]. This gives isoflurane cerebral protective properties as demonstrated by human studies of critical regional CBF during carotid clamping, in which isoflurane anaesthesia enabled CBF to be reduced to a greater extent before EEG changes occurred than did halothane or enflurane anaesthesia [11]. The high concentrations of isoflurane necessary to abolish cortical activity have no toxic effect on cerebral metabolic pathways [10], in contrast with high concentrations of halothane which induce cerebral acidosis [12]. The majority of human studies show that inspired concentrations of isoflurane of less than 1 % have little effect on ICP [13, 14] and any increase in ICP is counteracted easily by hyperventilation, but some patients with malignant brain tumours may show increases in ICP despite prior hyperventilation, particularly if the CAT scan shows a midline shift [15].

Because of the detrimental effects of convulsions on the brain, anaesthetic agents with epileptogenic properties should be avoided during intracranial surgery. Halothane does not cause abnormal EEG activity [16], whereas enflurane and isoflurane in concentrations up to 1–1.5 MAC have similar effects on the EEG, causing high voltage slow waves and hypersynchrony [16]. High amplitude spikes, spike and wave complexes, or both may occur with the administration of greater concentrations (> 1.5 MAC) of enflurane, particularly during hypocapnia and auditory stimulation [17]. In contrast, higher concentrations of isoflurane cause an isoelectric EEG [10]. Isoflurane does not cause the prolonged disturbances of the EEG which are reported following enflurane [18], but there are two case reports of convulsions during isoflurane anaesthesia in patients without neurological disease [19, 20]. A retrospective study in the author's department showed that 8 % of patients had convulsions in the first 24 h after craniotomy when enflurane was the volatile agent used, compared with 14 % when isoflurane was administered. This was not a statistically significant difference and indicates that postoperative convulsions are no more likely with enflurane than with isoflurane.

Volatile anaesthetic agents are contraindicated for induction of anaesthesia in patients with increased ICP, except in very young children when the sutures are not fused and there is more capacity for expansion of the cranial contents. In addition to the cerebral vasodilatation caused by high concentrations of volatile agents and their depressant effect on ventilation, an inhalation induction of anaesthesia almost always has an excitement phase which is associated with an increase in $CMRo_2$ and ICP. Clearly, this is undesirable in anaesthesia for craniotomy because, in addition to increasing ICP, it causes cerebral congestion which may take some time to settle. However, isoflurane or enflurane, in concentrations less than 1 MAC, could be used safely to supplement nitrous oxide immediately after i.v. induction of anaesthesia, provided that hyperventilation is undertaken concurrently. Halothane should be avoided until the dura is opened and then should be introduced only after hyperventilation for at least 10 min [4]. During maintenance of anaesthesia, volatile agents help to avoid recall of intraoperative events, potentiate the non-depolarizing neuromuscular blockers thereby reducing the chance of coughing or straining, and help to prevent sudden large increases in arterial pressure. Volatile agents attenuate the increase in arterial pressure associated with tracheal intubation and, because they reduce arterial pressure, may be used to facilitate hypotensive anaesthesia.

Following investigations in the 1960s which showed that volatile anaesthetic agents increased ICP, their use in neurosurgery has been controversial. It is now clear that volatile agents may be used safely either as the main anaesthetic or to supplement nitrous oxide and opioid anaesthesia for intracranial surgery, and have properties which are useful in this situation. However, in the presence of a large intracranial mass lesion or other cause of increased ICP when a small increase in CBV may cause a precipitous increase in ICP, the choice of anaesthetic agent is more critical and an i.v. infusion of an agent such as propofol, which reduces CBF, offers definite advantages over volatile agents. Halothane causes marked increases in CBF and ICP and its role in neurosurgical anaesthesia is limited. Enflurane in concentrations less than 1 MAC should not be discarded because it has little effect on CBF and ICP, and there is no clinical evidence that, in these concentrations, it causes an increased incidence of perioperative convulsions. Although isoflurane may occasionally cause convulsions, present evidence shows that it is the best of the available volatile agents for use in neurosurgery because it reduces CMRo_2 and has a cerebral protective effect; in the low concentrations used normally during relaxant anaesthesia, it has little effect on CBF and ICP, and it does not affect CSF production and absorption. Sevoflurane, another halogenated ether, has effects similar to those of isoflurane on the cranial content of rabbits [21], but studies in man are required to evaluate its place in anaesthesia for neurosurgery.

E. Moss

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Br. J. Anaesth. (1989), **63**, 7–11

PRIMING WITH ALCURONIUM AND TUBOCURARINE ACCELERATES THE ONSET OF NEUROMUSCULAR BLOCK†

B. J. POLLARD

SUMMARY

The individual rate of onset of action of tubocurarine and alcuronium has been examined with and without a priming dose of the same agent or the other agent, by measurement of changes in the evoked compound electromyogram of the adductor pollicis muscle. Priming was associated with acceleration of the onset of neuromuscular block.

The ideal neuromuscular blocking agent should have a rapid onset of action and a non-depolarizing character [1]. In order to accelerate the rate of onset of action, several techniques have been described, including the administration of a large bolus dose several times that required to achieve full neuromuscular block [2], and preliminary priming with a small subparalytic dose of the drug [3]. For optimum effect using the technique of priming, the first dose should be approximately 15–20% of the intubating dose [4], which may cause symptoms of partial neuromuscular block in a significant proportion of the population [5]. It has been suggested also that the priming dose should be given 6–8 min before the main intubating dose for the greatest effect [4].

Combination of some pairs of non-depolarizing neuromuscular blocking agents exhibits synergism of action [6–8]. It is possible that priming one blocking drug with a different synergistic agent may also accelerate the rate of onset. This has been tested with combinations of pancuronium, tubocurarine and atracurium and the onset of neuromuscular block was increased, but to only a limited extent [9, 10]. It was decided, therefore, to examine further this technique of synergistic priming, with a pair of non-depolarizing neuromuscular blocking agents which exhibit strong synergy of action—tubocurarine and alcuronium [6].

PATIENTS AND METHODS

Informed consent was obtained from patients (ASA I or II) in whom the anaesthetic technique of choice would include neuromuscular block. Ethics Committee approval was granted for the study. Patients with a known history of renal, hepatic, neurological or neuromuscular disorder and those taking drugs known to affect neuromuscular transmission were excluded. Each patient was premedicated with diazepam by mouth 1 h before operation. In the anaesthetic room, surface electrodes were placed over the ulnar nerve at the wrist and over the ipsilateral adductor pollicis muscle, after the skin was cleaned with acetone. The electrodes were connected to a Medelec MS6 system and the evoked compound electromyogram (EMG) from the adductor pollicis muscle was displayed and recorded.

Anaesthesia was induced with a sleep dose of thiopentone and the nerve stimulated with trains of four stimuli (0.2 ms duration, supramaximal voltage) at 12-s intervals. The preliminary (priming) dose of blocker was given, and the main intubating dose 3 min later. During this time, anaesthesia was maintained with increments of thiopentone as required and ventilation assisted with 67% nitrous oxide in oxygen, maintaining normocapnia.

The intubating doses of tubocurarine and alcuronium were 0.5 mg kg^{-1} and 0.25 mg kg^{-1}, respectively; priming doses were 10% of the

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This article is accompanied by Editorial I.

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†An abstract of this work was presented to the Anaesthetic Research Society, November 1987.

TABLE I. *Allocation and doses of neuromuscular blocking agents*

Group	Preliminary agent	Intubating agent
1	Saline	Tubocurarine 0.5 mg kg^{-1}
2	Tubocurarine 0.05 mg kg^{-1}	Tubocurarine 0.5 mg kg^{-1}
3	Alcuronium 0.025 mg kg^{-1}	Tubocurarine 0.5 mg kg^{-1}
4	Saline	Alcuronium 0.25 mg kg^{-1}
5	Alcuronium 0.025 mg kg^{-1}	Alcuronium 0.25 mg kg^{-1}
6	Tubocurarine 0.05 mg kg^{-1}	Alcuronium 0.25 mg kg^{-1}
7	Saline	Tubocurarine 0.55 mg kg^{-1}
8	Saline	Alcuronium 0.275 mg kg^{-1}

intubating doses. Thus six groups were created: an intubating dose of each relaxant preceded by a priming dose of the same drug, the second agent, or normal saline (table I). Two further groups (7 and 8) were included also, using normal saline as the priming agent and an intubating dose equivalent to the sum of the first and second doses in the previous groups; that is, 110% of the intubating dose. The patients were allocated randomly to the respective groups.

The degree of neuromuscular block was calculated as the percentage change in EMG amplitude of the first response of the train-of-four (T1) from that before administration of any relaxant (T0) and also the train-of-four ratio (amplitude of fourth response/amplitude of first response: T4/T1).

Data from the pairs of control groups (1 and 7; 4 and 8) were analysed using one-way analysis of variance at each time point. The aggregated data from groups 1 and 7 together were compared with those from groups 4 and 8 together. Two-way analysis of variance was carried out at each time point to see if there was any difference between the three agents given first, between the two agents given second, and to determine if the magnitude of any difference between the means was dependent on which drug was given first.

RESULTS

There were no significant differences between the groups with respect to mean age, weight and sex ratio (table II). There was no detectable change in neuromuscular transmission resulting from administration of the priming dose. There was no difference between the mean maximum neuromuscular block reached in each group (table II). A neuromuscular block of 100% was exceeded only in four patients, two each in groups 3 and 6. There was no significant difference between the two control groups at any time for the change in

TABLE II. *Demographic patient data and maximum block reached (means (SEM))*

Group	Age (yr)	Weight (kg)	Sex (F:M)	Maximum block (%)
1	37.1(3.4)	70.1(5.3)	6:2	90.6(1.9)
2	44.1(6.2)	62.1(3.2)	7:1	91.6(2.7)
3	36.4(4.7)	65.6(4.9)	7:1	96.2(1.3)
4	39.0(4.7)	72.9(7.1)	6:2	91.9(1.7)
5	34.5(3.5)	64.2(3.8)	7:1	93.1(2.0)
6	38.0(6.5)	61.0(1.8)	7:1	97.0(0.9)
7	32.0(3.7)	69.6(3.1)	6:2	92.5(1.7)
8	37.2(7.3)	55.8(2.6)	7:1	93.5(2.8)

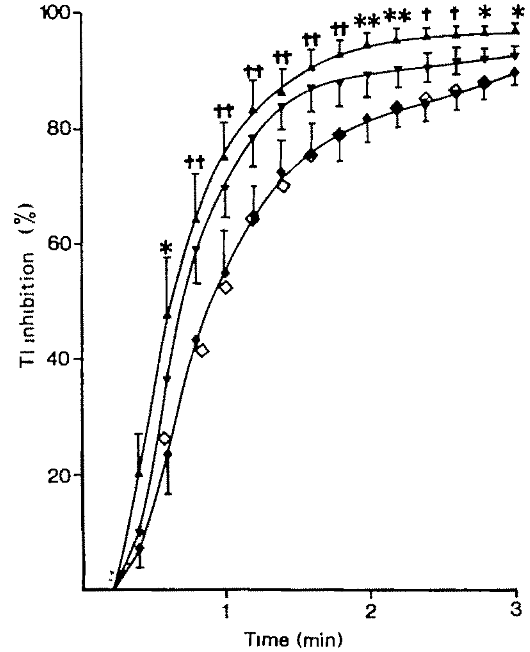

FIG. 1. Percent reduction in EMG amplitude of first response of train-of-four (T1) with time for tubocurarine as the intubating relaxant. ◆ = Saline–tubocurarine 0.5 mg kg^{-1}; ◇ = saline–tubocurarine 0.55 mg kg^{-1}; ▼ = tubocurarine–tubocurarine; ▲ = alcuronium–tubocurarine. Significant differences from saline groups (no priming): $*P < 0.05$; $**P < 0.01$; $\dagger P < 0.025$; $\dagger\dagger P < 0.005$.

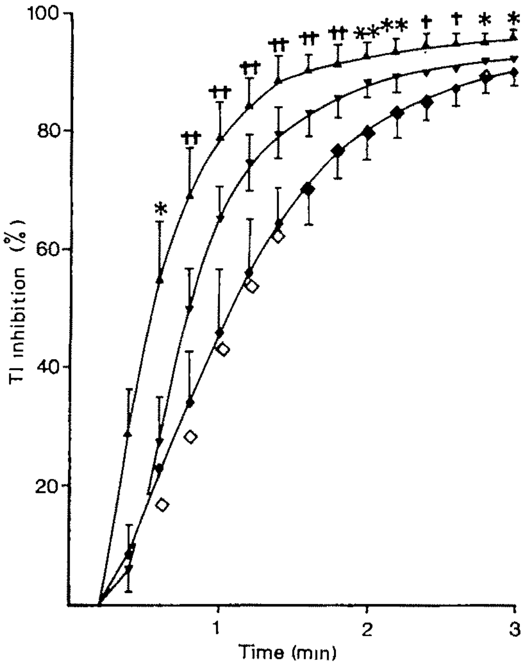

FIG. 2. Percent reduction in EMG amplitude of first response of train-of-four (T1) with time for alcuronium as the intubating relaxant. ◆ = Saline–alcuronium 0.25 mg kg^{-1}; ◇ = saline–alcuronium 0.275 mg kg^{-1}; ▼ = alcuronium–alcuronium; ▲ = tubocurarine–alcuronium. Significant differences from saline group (no priming): *$P < 0.05$; **$P < 0.01$; †$P < 0.025$; ††$P < 0.005$.

T1:T0 ratio for those groups in which tubocurarine was used to facilitate intubation (fig. 1). Both of the lines for the two groups in which priming was used (groups 2 and 3) were significantly different from the control lines at the points indicated (fig. 1). Although the line for group 3 (alcuronium before tubocurarine) lies to the left of that for group 2 (tubocurarine before tubocurarine) there was no significant difference between these two groups.

Figure 2 illustrates data for those patients in whom alcuronium facilitated intubation; it resembles figure 1. There was no significant difference between the two control lines at any time. The lines for the two groups in which priming was used (groups 5 and 6) are significantly different from the control lines as indicated on the figure. Although the line for group 6 (tubocurarine before alcuronium) lies markedly to the left of that for group 5 (alcuronium before alcuronium), there was no significant difference.

Comparison of the tubocurarine and alcuronium control groups using the aggregated data of groups 1 and 7 together and groups 4 and 8 together revealed no significant difference at any time between the rates of onset of tubocurarine and alcuronium when given alone.

The changes in mean train-of-four ratio with changes in T1:T0 are shown in figure 3 (control groups 1 and 4: tubocurarine alone and alcuro-

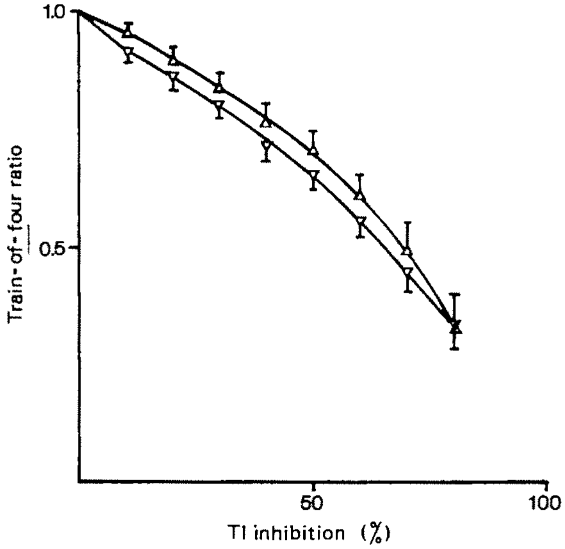

FIG. 3. Change in train-of-four ratio with change in T1 amplitude for tubocurarine and alcuronium without priming. ▽ = Saline–tubocurarine; △ = saline–alcuronium.

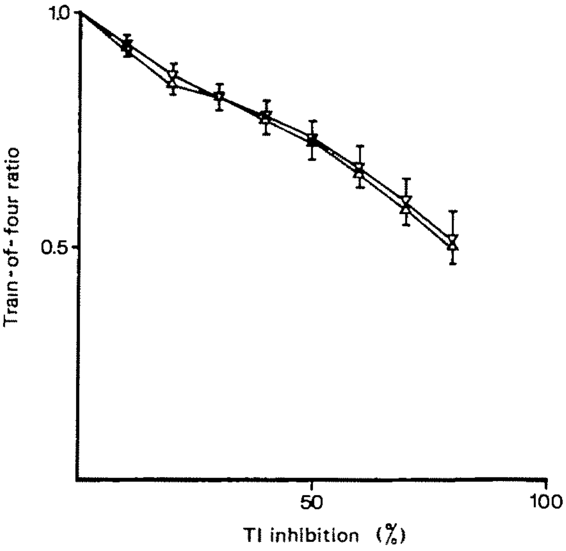

FIG. 4. Change in train-of-four ratio with change in T1 amplitude for tubocurarine and alcuronium when each primed with the other. ▽ = Alcuronium–tubocurarine; △ = tubocurarine–alcuronium.

nium alone) and figure 4 (groups 3 and 6, in which each agent was primed with the second one). Tubocurarine demonstrated slightly more fade than alcuronium, a difference which was not significant and not present when priming with the second agent had been used.

DISCUSSION

Tubocurarine and alcuronium were chosen because they are known to exhibit synergism of action which is stronger than tubocurarine and pancuronium *in vitro* [6]. In order to compare equipotent doses, the ED_{95} of each was selected as the intubating dose with a priming dose of 10% of the ED_{95}.

Savarese [11] suggested a dose of 0.51 mg kg^{-1} as the ED_{95} for tubocurarine and Shanks [12] an overall mean for all published data of 0.48 mg kg^{-1}. A value of 0.50 mg kg^{-1} was therefore chosen for ease of calculation. There are fewer data for alcuronium than for tubocurarine. Shanks [12] suggested an ED_{95} of 0.22 mg kg^{-1} and Lund and Stovner [13] suggested a relative potency of alcuronium and tubocurarine as 1.8:1. A value of 0.25 mg kg^{-1} was chosen, therefore, as an ED_{95} for this study. It is clear from inspection of the mean maximum neuromuscular block reached (table II) that these two doses were near to equivalence.

There is a large margin of safety in neuromuscular transmission such that approximately 75% of receptors have to be occupied by antagonist molecules before failure of transmission begins [14]. After a single bolus dose, receptor occupancy has to increase from zero to more than 75% before depression of T1 is seen. If a small priming dose is administered, sufficient to produce receptor occupancy of just less than 75%, the addition of a second intubating dose has to increase receptor occupancy just above this figure. An additional pharmacokinetic mechanism has been proposed also [15]. Because the concentration of blocking drug at the neuromuscular junction determines neuromuscular block, predosing allows that drug to reach an effective concentration sooner, thereby accelerating the onset of block. Whichever mechanism is operating, onset would be expected to be more rapid, as observed in this study and in previous studies with tubocurarine [4, 16], alcuronium [4, 17], vecuronium [18], atracurium [19, 20] and pancuronium [3, 21].

In addition to the classical postjunctional acetylcholine receptors, other acetylcholine receptor systems exist on the prejunctional region [22] and different neuromuscular blocking drugs are thought to possess a unique spectrum of actions on the whole receptor system. It is likely that synergism between some pairs of non-depolarizing neuromuscular blocking agents appears when two agents with dissimilar activity spectra are combined. The acceleration of neuromuscular block resulting from the priming dose of the second agent in this study was slightly greater than when the relaxant was primed with itself. If a pharmacokinetic effect alone is proposed for priming, one might expect priming with a different agent to be no more effective, or even less effective than priming with itself. This was not observed in the present study. It is interesting to note that the rate of onset of alcuronium was accelerated to a greater extent by tubocurarine than was tubocurarine by alcuronium.

Although no detectable block was found to result from the priming dose in this study, administration of a small dose of a non-depolarizing neuromuscular blocking agent has been shown to cause unpleasant partial paralysis in some patients [5, 23]. Under some circumstances, this might be hazardous [24].

The increase in rate of onset when alcuronium and tubocurarine are primed with each other is marked, 80% neuromuscular block being reached in just over 60 s. With suxamethonium 1 mg kg^{-1} 100% block is reached in approximately 70 s [25]. The time response curve with suxamethonium is steeper, however, and suxamethonium causes a more profound block.

ACKNOWLEDGEMENT

The author is grateful to Miss Linda Hunt, Lecturer in Medical Statistics, University of Manchester, for her assistance in the analysis of these data.

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Br. J. Anaesth. (1989), **63**, 12–21

INFLUENCE OF THIOPENTONE ON UPPER AIRWAY MUSCLES

G. B. DRUMMOND

SUMMARY

Surface electromyograms of tongue and neck muscles were measured in 14 patients before surgery under general anaesthesia to assess their relative importance in the maintenance of airway patency during sedation with i.v. thiopentone. During the i.v. administration of successive 50-mg doses of thiopentone, the mean activity of the genioglossus, sternothyroid and sternohyoid (strap muscles), and scalene muscles decreased. There was a wide variation in response, with frequent activation of the scalene and strap muscles after small doses of thiopentone. The activity of the strap and scalene muscles changed from a tonic pattern to activity in phase with inspiration. Airway obstruction was frequent and accompanied by significant increases in phasic muscle action which did not overcome the obstruction. The pattern of changes observed suggests that loss of tonic activity in the sternothyroid and sternohyoid muscles is associated with airway obstruction.

The patency of the upper airway is maintained well in the conscious subject, irrespective of the position of the head and neck, by active mechanisms that involve muscles inserted into the hyoid and thyroid cartilages [1]. In contrast, the airway of the anaesthetized or unconscious subject is susceptible to obstruction, even if anaesthesia is deliberately maintained at a light level [2]. Studies in anaesthetized paralysed patients suggested that the tongue was the most frequent cause of this obstruction [3], and many manoeuvres used by anaesthetists to improve airway patency are considered to prevent airway obstruction by the tongue. In animal experiments, activity of the genioglossus and geniohyoid muscles is associated with the maintenance of airway patency [4], and reduced activity of the genioglossus in man has been implicated in the pathogenesis of airway occlusion during sleep [5, 6]. Anaesthetic agents cause greater depression of the activity of these muscles than of the diaphragm [7–10].

However, in the anaesthetized subject, obstruction of the upper airways is caused less commonly by the tongue than by the epiglottis [11]. Although genioglossus activity could indicate activity of the upper airway muscles in general, it is possible that other muscles may be equally or more important in maintaining airway patency. This possibility is supported by the fact that, although airway obstruction during sleep causes reflex activation of the genioglossus [12, 13], this increased activity may not be sufficient to restore patency of the airway [14].

This study was designed to assess the pattern of changes in action of muscles of the upper airway during slow induction of anaesthesia and observe what changes were associated with the onset of airway obstruction, if this occurred. In addition to recording activity from the genioglossus, we assessed the activity of muscles likely to influence the position of the hyoid cartilage, as hyoid position appears to be important in control of airway patency in anaesthetized man [11]. Activity in muscles with a predominantly postural and ventilatory role was measured also.

PATIENTS AND METHODS

The study was approved by the Area Ethics Committee. Fourteen patients (seven male and seven female, mean (SD) age 51 (16) yr, height 169 (6) cm, weight 111 (26) % expected [15]) were studied, selected from patients about to undergo elective surgery under general anaesthesia. No patient had clinical evidence of respiratory or

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Accepted for Publication: January 30, 1989.

neuromuscular disease, or was at risk from regurgitation. Verbal consent was obtained on the day before the study.

Each patient received premedication with temazepam 20 mg orally, 1 h before the study, which was carried out in a quiet, warm room. An i.v. infusion of Hartmann's solution was started and an extension tube attached so that injections could be made without disturbing the patient. After the electrodes (see below) had been connected, the patient was encouraged to relax in the supine position, with the head in the midline resting on a single soft pillow, and the arms supported at the sides. The recording apparatus was kept out of sight of the patient, so that there was no opportunity for visual feedback from the EMG display.

Skin over the scalenes, under the chin, in the midline below the thyroid prominence, and over the clavicle was prepared with abrasive electrode jelly followed by acetone. After this form of preparation, inter-electrode impedance is less than 2 KΩ. Two disposable pregelled silver–silver chloride electrodes (Medicotest R-00-S) with a gel diameter of 1 cm were cut so that they could be applied over each muscle with centres 3 cm apart. For the tongue, the first electrode was placed in the midline immediately posterior to the lower edge of the mandible, and the second immediately posterior to this. This modification of the method of Sauerland and colleagues [16] had been found, in preliminary studies, to give consistently large signals associated with tongue protrusion. Electrodes were placed also in line over the mass of the scalenus medius at the most caudal level at which the muscle could be felt. The third set of electrodes was placed in the midline, in an axial line immediately caudal to the thyroid prominence. In subjects in whom the sternomastoid muscles were felt to be encroaching on this position, the cranial electrode was placed directly over the thyroid cartilage, so that the lower electrode could be moved cranially, away from the insertion of the sternomastoid muscles. Electrodes in this position record activity mainly from the underlying sternothyroid and sternohyoid muscles. Verification of accurate placement of these electrodes was possible in patients who subsequently underwent thyroid operations. However, because the source of the signals from the submental and midline neck electrodes cannot be established exactly, the signals from these electrodes are referred to as from the "tongue" and "strap muscles" of the neck, rather than from specific muscles. A single reference electrode was placed over the clavicle. This electrode was used also as a reference electrode for the ECG.

The EMG signals were recorded through 5-cm leads connected to a buffer amplifier (NL101) and amplified with a matching differential amplifier (NL104, Digitimer Ltd). The signals were passed through a bandpass filter (NL125) between 10 and 5000 Hz and recorded with the ECG and a commentary channel on FM tape (Digitimer D146) for subsequent analysis. In addition to recording observations, the commentary channel was used to signal the phases of ventilation by observing chest movements or respiratory sounds and switching the microphone during inspiration. Tape recordings were made at 9.5 cm s^{-1}, which gave a linear frequency response from 0 to 2.5 KHz. The amplifier gains were adjusted to obtain satisfactory signal amplitudes while the patient was asked to perform three separate manoeuvres, to obtain an estimate of the maximal activity that could be recorded from the three sets of electrodes. For the tongue, the patient was asked to protrude the tongue as forcibly as possible. For the strap muscles, the patient was asked to swallow, which gave a reproducible degree of activity, although preliminary studies in trained subjects had shown that these muscles could be activated more than this by voluntary activation after training. To activate the scalene muscles, the patient was encouraged to take two maximal inspirations. The amplifier gains were increased to measure the spontaneous resting activity and the patient was allowed to relax for at least 5 min, before administration of drugs was started.

Thiopentone was administered i.v. in 50-mg bolus doses every 30 s, to a maximum dose of 300 mg, and the activity of the muscles recorded continuously. Immediately before each subsequent dose, the presence of the eye-lash reflex was assessed and note made if ventilation was noisy or obstructed. Airway obstruction was judged to be present if the gas flow felt at the mouth or the nose became markedly reduced, despite continued ventilatory movement, or if the pattern of chest wall movement became abnormal. When one of these endpoints had been reached, no further thiopentone was given for 2 min. If ventilation was noisy or obstructed, the chin was lifted until respiration became clear. Occasionally, this stimulus caused arousal of the patient. If the airway obstruction did not resolve within this time, the study was discontinued. After the thiopentone effects had been recorded, oxygen was administered by mask and then, if necessary, a further thiopentone 100 mg was given to ensure unconsciousness before giving suxamethonium 1.5 mg kg^{-1} i.v. to facilitate tracheal intubation. The recording was continued so that a "zero activity" signal after neuromuscular block could be obtained.

The signals were analysed by replay through a delay unit and gating device triggered by the non-delayed ECG recording, so that the ECG artefact on the EMG signal could be gated out, similar to the device used by Muller and colleagues [17]. The signal was then passed through a 5–1000 Hz bandpass filter, rectified, integrated with a "leaky integrator" (Digitimer NL703) set at a time constant of 100 ms, and recorded with a UV galvanometer recorder (Bell and Howell 5–137). A calibration signal of 1 V was passed through the delay system and integrator. Zero activity was taken as the signal obtained from integration of the recording obtained after administration of suxamethonium. Measurements of activity were made over 10 s immediately before administration of thiopentone. In those patients in whom activity increased in association with airway obstruction, measurements were made of the peak activity and again after the airway obstruction had been overcome by tilting the head back.

EMG activity was calculated in terms of averaged root mean square voltage (μV) and expressed as a percentage of the activity of that muscle in the awake state. When activity was phasic, in time with ventilation, maximum and minimum activity in each ventilatory cycle was measured. "Phasic activity" was considered arbitrarily to be present when there was a variation of amplitude in the integrated signal of more than 50% between inspiration and expiration. As the percentage values had a clearly skewed distribution pattern, they are presented on logarithmic scales and mean values have been calulated using the logarithm of the actual values. (For the purpose of these calculations, and in the figures, zero values were assigned an arbitrary value of 5%). The results have been converted back to the original values for presentation; consequently, the SD values given indicate both a lower and an upper value. Statistical analysis was with the Wilcoxon signed rank test for paired values [18], using a probability of < 0.05 to indicate significance.

TABLE I. *Muscle activity in the conscious state in the three muscle groups (mean (range of log SD values))*

	Tongue	Strap	Scalene
Absolute (μV)	4.6 (2.3–9.1)	5.9 (2.4–14.6)	5.8 (2.2–14.9)
Percent maximum	4 (1–15)	18 (8–42)	12 (5–31)

RESULTS

The resting activity of the muscle groups varied considerably, both in absolute terms and expressed as a fraction of the activity noted during maximum voluntary activation (table I). Changes in activity after administration of thiopentone were interpreted most readily in relation to the activity found in the conscious resting state, rather than in terms of absolute electrical activity or in relation to the maximal activity recorded. In all subjects, muscle activity was tonic in the conscious state, although in two patients some phasic activity in time with inspiration was noted in addition to tonic activity in the scalene muscles. In one conscious subject, no activity was found in the scalene muscle, but activity was observed after thiopentone 50 mg. The data for the scalene muscle in this subject cannot be presented as a fraction of the awake activity.

As expected, the response of the patients to the fixed dose regimen of thiopentone was variable. The quantity of thiopentone given before airway obstruction persisted was as little as 100 mg in two patients. Ten subjects received at least 200 mg, and five received 250 mg or more. The changes in activity of the three muscle groups after successive doses of thiopentone are summarized in figure 1, which shows the activity at each dose interval, for those subjects who received the dose. If the activity was phasic, the value shown is the inspiratory peak value. Different patterns of changes in activity were noted. Transient tonic increases in activity occurred, particularly in the strap muscles (six patients), but also in the scalene muscle group (four patients). Three patients showed increases in activities in both muscle groups. In general, there was a progressive decrease in activity of the muscles with successive doses of thiopentone. In the case of the tongue, the decrease was significant after the first dose. However, in the other muscle groups, and after subsequent doses of thiopentone, there were no significant changes in maximum activity. The lack

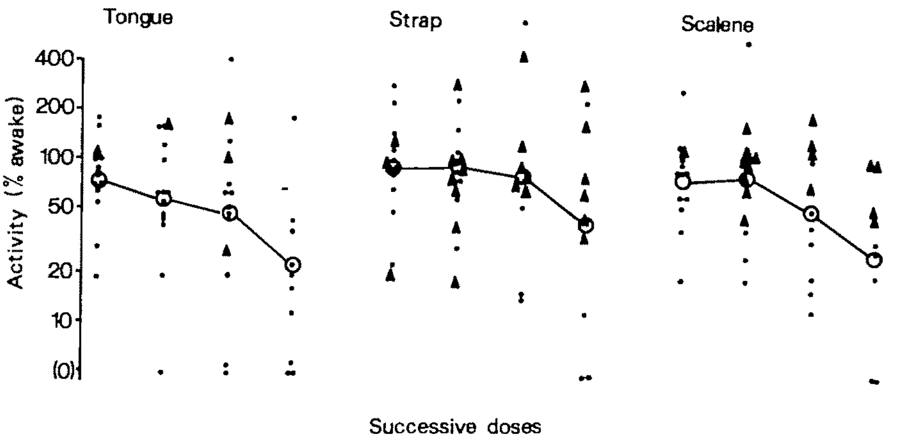

FIG. 1. Activity in the muscle groups in inspiration (integrated values expressed as % of the awake value) after successive doses of thiopentone, made in the absence of clinically apparent airway obstruction. ● = Subjects with tonic activity; ▲ = subjects with phasic activity; ○ = mean of log values.

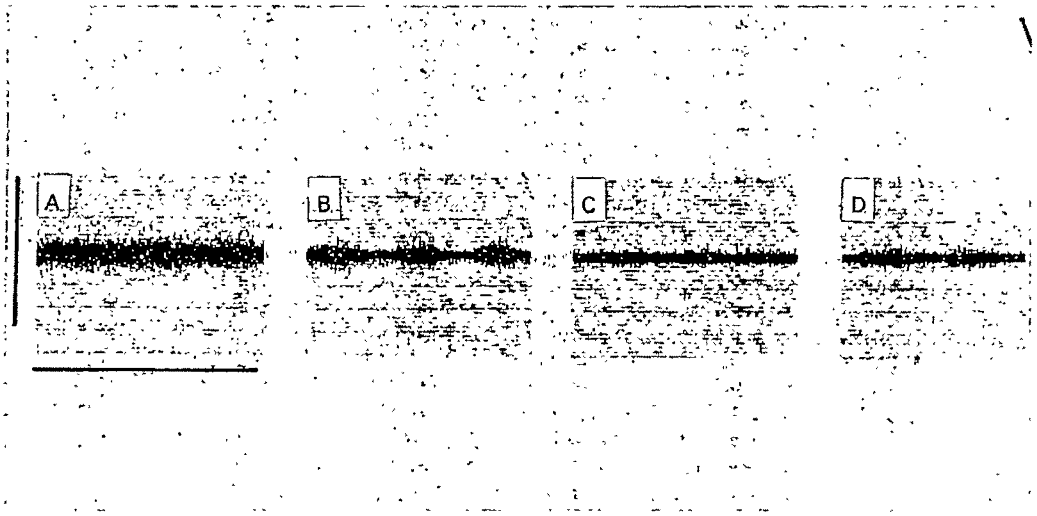

FIG. 2. Scalene muscle EMG in a representative patient. A: Awake. B: After thiopentone 100 mg, with noisy breathing. C: Airway supported, breathing clearly. D: Support released, breathing noisily again. Scale: 500 μV, 10 s.

of statistical significance could be attributed to two striking effects that contributed to marked variations in activity.

First, the action of the muscles changed from tonic to phasic. This change was particularly noticeable in the strap muscles. In the conscious state, activity in these muscles was universally tonic, whereas after thiopentone 150 mg, activity showed a phasic pattern in all but two subjects. In the scalene muscles, activity became phasic in nine patients. In the tongue, phasic activity was noted in only three subjects.

Second, the degree of muscle activity was related to the patency of the airway. If airway obstruction developed, the amplitude of phasic activity increased, and commonly decreased when obstruction was relieved (fig. 2). The strap muscles showed this pattern most commonly, although in three patients an increase in phasic action was observed in all three muscle groups

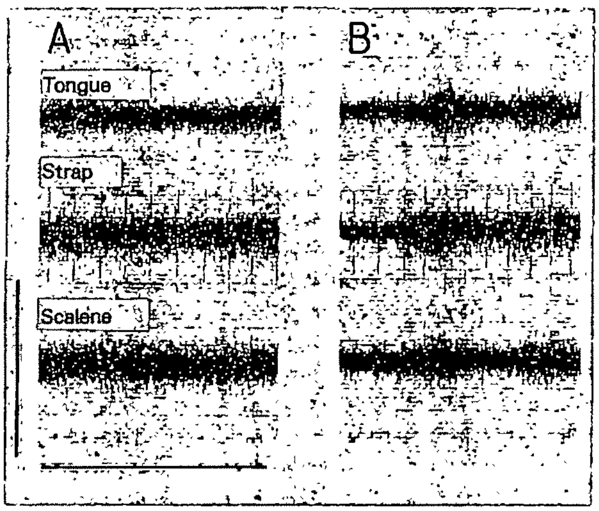

FIG. 3. EMG recording from a subject (one of three) in whom phasic activity developed in all three muscle groups in association with airway obstruction. A: Awake; B: airway obstruction. Scale: 100 μV, 10 s.

(fig. 3). When phasic activity increased in association with airway obstruction, the most marked increases were observed in the scalene muscle (fig. 4). In a patient in whom the activity of strap and scalene muscle developed progressively, before airway obstruction was relieved, the activities of the two groups increased proportionally in an approximately linear fashion (fig. 5).

Noisy breathing or airway obstruction developed in 10 patients. This occurred after thiopentone 50 mg in one patient, after 100 mg in five, and after 150 mg in the remaining four patients. No obvious factors that could be related to the development of airway obstruction, such as age, sex or obesity, were identified in this small and relatively homogenous sample of patients. The muscle activity noted in these patients before, during and after relief of the obstruction is shown in figure 6. The increases in strap muscle activity were significant ($P < 0.05$) but, although an increase in scalene muscle activity occurred in eight of the nine patients in whom values were available, these increases were not significant ($P < 0.1$).

No reduction of activity could be related directly to the onset of airway obstruction. Any such relationship was difficult to determine because noisy or inadequate breathing caused increasing muscle action that decreased when obstruction was relieved. However, there was no indication that reduced tongue activity led to airway obstruction: patients often breathed clearly when this activity was minimal and, conversely, obstruction was noted to occur when tongue activity remained present and tonic in pattern. As phasic activity in the strap muscles developed almost universally, this feature also cannot be related unequivocally to onset of obstruction: three of four patients who did not

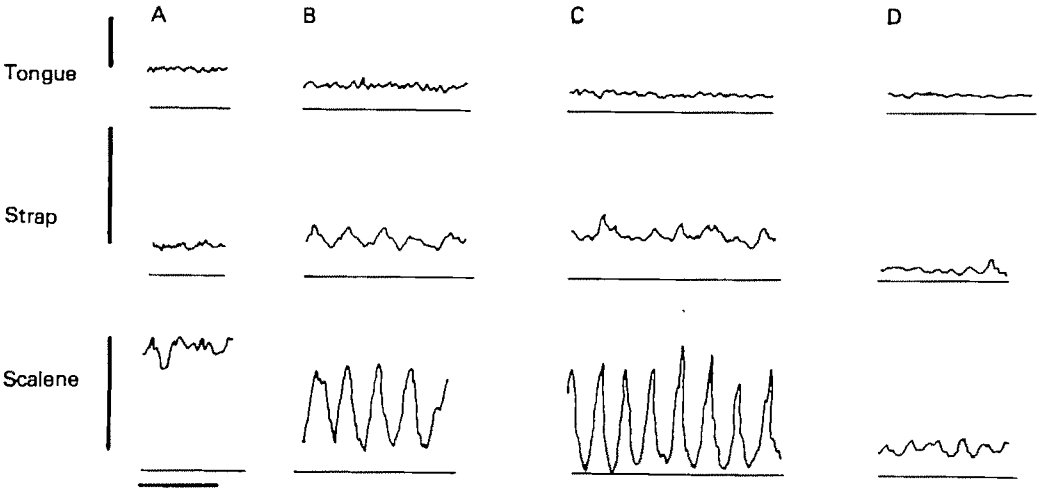

FIG. 4. Integrated EMG tracing from a patient showing the effects of airway obstruction. A: Awake. B: After thiopentone 100 mg, with noisy breathing. C: Airway obstruction. D: After a further 50 mg of thiopentone and with the airway supported. Scale: 10 μV, 10 s.

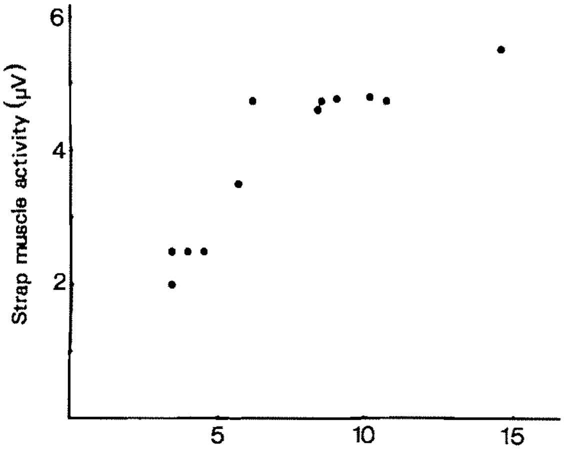

FIG. 5. Relationship between peak integrated EMG in strap and scalene muscles for successive breaths during the onset of increased activity associated with airway obstruction.

develop airway obstruction showed phasic strap muscle activity. In one patient, tonic activity persisted in the strap muscles after administration of thiopentone, and obstruction did not develop in this patient.

There was no evidence in any patient that the increasing activation of the muscles studied was sufficient to overcome the obstruction, which was always relieved shortly after its detection by the clinical staff involved in patient care. No clinically deleterious effects were noted in the course of the study.

DISCUSSION

Methods and subjects

Surface electrodes rather than needles were used in an attempt to reduce potential patient discomfort and apprehension, so that the degree of activity normally present in the premedicated patient would not have been exaggerated. The results indicate that, in these circumstances, the degree of muscle activity, although measureable, is small. Some of this reduction may have been caused by premedication, although no patient was noticeably sleepy during the study. However, surface electrodes have the disadvantage of not detecting signals from specific muscles. For example, using a similar technique for measurement of tongue activity, Sauerland and co-workers showed that a single submental electrode responded also to mouth opening and lip movements [16]. In the present study, both electrodes were placed in the submental area, and such responses were not seen. Large signals were obtained during tongue protrusion in all subjects. In addition, other movements that could have resulted in interference were not common in the patients during the period of the study.

Strap muscle activity could be identified reliably by the response obtained during swallowing, but contamination of the signal by activity

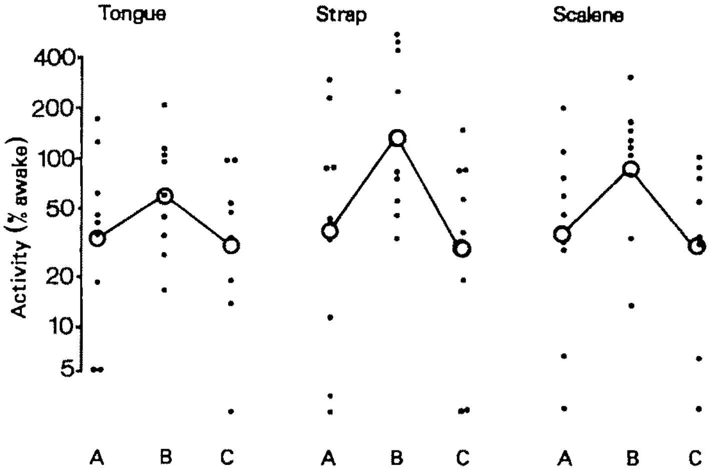

FIG. 6. Activity in the muscle groups in inspiration (integrated values expressed as % of the awake value) in patients with evidence of airway obstruction during sedation. A = Breathing clearly; B = during airway obstruction; C = after relief of obstruction.

from the sternomastoid muscles was possible. However, two observations suggest that this is unlikely to have markedly influenced the measurements. First, strong activation of the sternomastoid muscles, by raising the head, produced only minimal responses on the recordings. Second, although activity of the sternomastoid muscles is increased during induction of anaesthesia with thiopentone, the changes are usually less than 20% of the activity during maximal effort [19].

To assess airway obstruction objectively, a "non-invasive" measure of ventilation such as the respiratory inductive plethysmograph might have been useful. Electromyographic assessment of muscle action is less helpful, as the relationship between muscle activity and the pressures generated alter both with sleep state and with changes in airway resistance [20].However, when depressant drugs are given it is difficult to be certain if a reduction in gas flow has been caused by central depression or by airway obstruction. Assessment of the patency of the airway by clinical means proved to be adequate, often aided by the change of gas flow from the nasal to the oral route in association with loss of consciousness, and by the onset of noisy breathing before obstruction became more severe. Although it is possible that minor degrees of obstruction were not detected, it was not possible to devise a method by which such detection could be achieved without either causing stimulation to the nose or mouth, or necessitating topical anaesthesia of the airway, both of which may alter airway patency [21, 22].

Thiopentone was given in a fixed dose schedule with no regard for age, sex or weight, and it is likely that the effects of each bolus in individual patients were not strictly comparable. A fixed dose regime was used for several reasons. First, the patient population was relatively homogenous, with 10 of the 14 subjects aged between 30 and 60 yr. Second, although the variation in induction dose over the age range studied may be of the order of 40%, the standard deviation of the induction dose required within each gender and each decade of age is of the order of 30% [23], and hence the ability to predict closely the appropriate dose is not great. Third, thiopentone was administered at a slow rate, so that additional kinetic factors are likely to have influenced drug effect, and the ability to obtain consistent effects would become progressively less with successive doses. Finally, the study was intended to relate the changes in EMG activity to influences on the airway rather than assess the dose–effect relationship of thiopentone. It should be noted that the degree of drug effect achieved was not great: at the end of the study period, an eye-lash reflex was still present in seven subjects.

Both male and female patients were studied; nine were older than 40 yr. There seems to be little information other than clinical impression that airway patency during anaestheisa is more likely to be compromised in older, obese, male subjects. However, pharyngeal resistance is known to be greater in males, the elderly and the obese [24]. Although the conditions of sleep and anaesthesia are not strictly comparable, disturbances of breathing during sleep are more common in older subjects [25]. There is no general agreement on the relative susceptibility of men and women to the effects of sedatives on the airway, but men may be more sensitive. For example, alcohol selectively decreases genioglossus activity and increases upper airway resistance in men [26, 27] and this effect seems to be reduced by progesterone both in animals and in women [28, 29].

Findings and interpretation

Considerable evidence supports the concept of a complex co-ordinated reflex relationship between upper airway receptors, lung afferents and chemoreceptors on the one hand and, on the other, the activity of both the ventilatory muscles and the muscles of the upper airway.

The larynx is richly supplied with receptors that respond to gas flow and to contraction of upper airway muscles [30]. Negative pressure in the upper airway influences the activity and timing of the ventilatory muscles [31, 32] and the activity of several muscles in the upper airway [12, 33]. Chemical stimuli to respiration cause hypoglossal nerve activity to increase, with a pattern that differs in magnitude [34] and timing [35] from increases in diaphragmatic activity. Lung volume changes influence upper airway muscle activity [36]. When negative pressure is applied to the upper airway in anaesthetized rabbits, the sternothyroid and sternohyoid muscles develop phasic inspiratory activity [37]. The activity of the upper airway muscles precedes the activity of the diaphragm [36], and the volume increase of the upper airway occurs earlier than that of lung volume during inspiration [38]. Reflex responses associated with upper airway receptors may be reduced by subanaesthetic doses of pentobarbitone [39]. In addition, the response of the genioglossus seems to be more susceptible than the diaphragm to other forms of depression, such as sleep deprivation [40] or alcohol [26]. Finally, in normal subjects during sleep, upper airway resistance varies during induced variations in ventilation, in a manner that allows upper airway obstruction to develop when ventilatory drive is reduced [41].

Muscle activity observed in the awake patients was predominantly tonic. This is consistent with a previous study of the scalene muscles [19]. The pattern of activity noted in the tongue in this study was similar to that reported in an early descriptive study, in which electrodes were placed percutaneously into the tongue midway between hyoid and genial tubercle. In that study, electrodes placed more anteriorly in the tongue, via the mouth, showed some phasic activity in the conscious subject, although activity persisted throughout the cycle of ventilation [5]. Studies of neural activity in decerebrate or anaesthetized animals more commonly show phasic activity [7–9], but it must be noted that the neurogram represents the pattern of activation of all the muscles served by that nerve, and individual muscles may have different patterns of activation. Steady tonic electrical activity is observed frequently in the tongue, even with the use of i.m. electrodes in conscious man and animals [13, 35]. The change to phasic ventilatory activity of the strap and scalene muscles observed in this study after administration of barbiturates is similar to the change noted in the cricothyroid muscle in the rat after pentobarbitone [42].

Progressive increase in muscle activity in association with airway obstruction has been described in children [14] and adults [13] during sleep. In the present study, both the rate of increase, and the marked effects in the scalene muscles suggest that this response was caused by increasing chemical drive rather than by upper airway afferent mechanisms. Although the exact location is not clear, the site of airway obstruction in patients with sleep apnoea syndrome may be at the level of the soft palate [43], whereas during inhalation anaesthesia, obstruction occurs commonly in the hypopharynx [11]. Pharyngeal compliance is greater in subjects with sleep apnoea [44]. Application of positive airway pressure (CPAP) to the nose may reduce the frequency of obstructive apnoea during sleep and also reduces genioglossus muscle activation [45]. However, preliminary studies using nasal CPAP have not shown a useful effect in reversing the airway obstruction and increased muscle activity during barbiturate sedation [Drummond, unpublished observations].

The significance of the changes noted in the present study is difficult to determine without corroborative studies. EMG activity does not indicate directly the mechanical role of the muscle. For example, depending on the load to the muscle, increased EMG activity may be associated with increased tension in the muscle or shortening of the fibres, or both. The muscle could even lengthen, if the fibres were opposed by the simultaneous action of a muscle that could generate a greater force. Thus contraction of the diaphragm when the airway was occluded would reduce airway pressure that could pull in the tissues of the neck and lengthen the strap muscles, and decrease the pleural pressure which could act through the ribcage to lengthen the scalene muscles, despite a pattern of increased EMG activity in these muscles.

Because the activities of the different muscles of the upper airway show parallel changes, it does not necessarily follow that reduced activity of a particular muscle directly causes reduced airway patency, as this may merely be a phenomenon that occurs at the same time. However, there is evidence from animal studies that the sternohyoid and sternothyroid muscles do act directly to prevent airway collapse. Electrical stimulation of these muscles, and tension applied to the insertions of these muscles into the hyoid, reduce the tendency of the upper airway to collapse [46]. Increased volume of the upper airway is associated with shortening of the sternohyoid and geniohyoid muscles [47]. These animal studies, particularly the latter, are consistent with early observations in man using radiography [1] that muscle action is associated intimately with the maintenance of airway patency during changes in position of the head and neck, and with the more recent observations of Boidin in man during anaesthesia [11]. In Boidin's study, airway obstruction was associated most consistently with contact between the epiglottis and the posterior pharyngeal wall, and the motion of the epiglottis and hyoid are closely associated, and controlled by the neck strap muscles.

In the present study, patients continued to breathe clearly, despite marked reductions in tongue activity. On the other hand, airway obstruction could develop despite persistent tonic activity in the tongue. However, airway obstruction was associated with parallel increases in scalene and strap muscle activity (fig. 5). For example, if thiopentone reduced strap muscle action, which led to airway obstruction, this would be associated with an increase in strap muscle activity. Unless the temporal relationship of loss of activity, obstruction and then increased activity were clear, it is unlikely that an exact relationship between activity of a specific muscle and airway patency could be detected other than as a fleeting event. The change of activity to a phasic pattern may be relevant: loss of tone during expiration may allow collapse to occur, which could not be overcome by increasing activity during inspiration, if the inspiratory muscles are acting to reduce intraluminal pressure at the same time. Preliminary studies using ultrasound imaging suggest that, during administration of thiopentone in man, airway obstruction can occur despite minimal and inconsistent movements of the main mass of the tongue [Abernethy and Drummond, unpublished observations]. These considerations suggest that observations of other muscles, of the effects of other anaesthetic agents, and using other techniques of assessment of muscle action, are necessary to determine the exact mechanisms of airway obstruction during anaesthesia.

In conclusion, this study suggests, but does not prove, that a change in the pattern of activity of the upper airway muscles, rather than a reduction in the magnitude of their activation, may be responsible for the development of airway obstruction during administration of thiopentone. Increased activation occurs in association with obstruction, but is ineffective in relieving obstruction when it has occurred.

ACKNOWLEDGEMENTS

The author wishes to thank Miss Elaine Campbell for constructing the delay and gating device which made measurements of these small signals practicable, and the Biomedical Research Committee of the Scottish Home and Health Department, for the grant to purchase the measuring and recording equipment.

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Br. J. Anaesth. (1989), **63**, 22–30

AUTOMATIC ARTERIAL PRESSURE REGULATION USING ISOFLURANE: COMPARISON WITH MANUAL CONTROL

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The use of induced hypotension in anaesthesia requires meticulous care and constant attention to maintain arterial pressure at a precise value [1]. It may be advantageous to use closed-loop control systems capable of maintaining arterial pressure at a predetermined value by automatically adjusting the rate of infusion of a vasoactive drug. Automatic controllers are capable of equalling the anaesthetist's performance in maintaining a stable pressure, but are not susceptible to the problems of inattention, fatigue and distraction [2–4]. The performance of simple fixed-gain Proportional-Integral-Derivative (PID) controllers is limited by: the variability in patient response to vasoactive drugs; changes in an individual patient's sensitivity with time; differences in individual patient latency of response to drugs; and changing levels of surgical stimulation [5]. Based on the generalized minimum-variance algorithms of Clarke and Gawthrop [6], a self-tuning closed-loop controller (STC) has been developed which is able to adapt to these problems, and has been used previously with infusions of both sodium nitroprusside (SNP) [7] and phenylephrine [8, 9]. The design of a computer driven, motorized vaporizer has allowed the alternative use of the inhalation agents to induce hypotension. This study reports on the use of isoflurane by the STC to regulate mean arterial pressure (MAP) in patients undergoing ENT surgery. The effects of differing background anaesthetics on the quality of control is examined and a comparison made with a manually controlled group.

SUMMARY

A self-tuning, closed-loop controller, based on the algorithm of Clarke and Gawthrop, was used to regulate the inspired concentration of isoflurane to reduce arterial pressure electively in 33 patients undergoing ENT surgery. The patients were allocated randomly to one of four groups and received differing doses of fentanyl and labetalol to vary the range of sensitivities to the hypotensive action of isoflurane. The performance of the controller was evaluated at two target arterial pressures (AP), by its response to simulated changes in AP and by a comparison with a further group of eight patients with manual control of AP. The controller's undershoot of AP (range 2.8±0.5–4.5±1.3 mm Hg) and % time spent within ±5 mm Hg of the target AP (range 83±3.4–89±2.2%) were acceptable and equalled the manual performance figures (range 3.3±0.8 mm Hg; 90±5%). The regulation of induced hypotension in all four groups was rapid, accurate, stable and reproducible.

PATIENTS AND METHODS

The STC was studied in 33 patients (ages 17–56 yr, ASA I–II) requiring induced hypotension for either nasal or middle ear surgery. In another eight patients (ages 18–43 yr, ASA I–II) hypotension was controlled manually for comparison. Patients with cardiorespiratory, endocrine or central nervous system diseases were excluded from the study. Ethics Committee approval and informed patient consent were obtained. All patients were premedicated 90 min before surgery with temazepam 20 mg (or 30 mg for those weighing more than 75 kg). The 33 STC patients were allocated randomly to one of four groups according to the dose of fentanyl and labetalol used (table I). The manual control group received

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low dose fentanyl plus labetalol (as did STC group 3).

Under local anaesthesia, catheters were inserted via the antecubital fossa into a central vein (16-gauge Wallace) and brachial artery (18-gauge Abbocath). Anaesthesia was induced with thiopentone 4 mg kg^{-1}, followed by vecuronium 0.1 mg kg^{-1} and fentanyl as required by the programme. After tracheal intubation anaesthesia was maintained with the appropriate infusion of fentanyl and 50% nitrous oxide in oxygen. End-tidal carbon dioxide concentration was monitored (Gould-Godart Capnograph Mk1) and maintained in the range 4.9–5.6 kPa by adjusting the fresh gas flow to a Bain system and Nuffield 200 ventilator. Hartmann's solution was given i.v. at 20 ml kg^{-1} h^{-1} for 30 min and at 2 ml kg^{-1} h^{-1} thereafter. If allocated to a labetalol group, the patient received a bolus dose and an infusion started before surgery and continued until the completion of the study.

The MAP was read by BBC microcomputer via the arterial catheter, a pressure transducer (Gould P231) zeroed to the mastoid process, arterial pressure monitor (Hewlett–Packard 78205A) and an Analogue to Digital Converter (ADC). A Cyprane vaporizer was modified by the addition of an electric servomotor and clutch controlled by the BBC computer via a Digital to Analogue Converter. The 0–5% vaporizer concentration range was allocated to 64 positions determined by a potentiometer contained within the drive unit. As the concentration selector scale is non-linear, a table was used to determine the position of the potentiometer equivalent to the required inspired isoflurane concentration. The accuracy of the vaporizer was verified by mass spectrometry (BOC RMS3).

TABLE I. *Anaesthetic doses*

	Fentanyl	Labetalol
Group 1		
Bolus	2.5 μg kg^{-1}	—
Infusion	1.5 μg kg^{-1} h^{-1}	—
Group 2		
Bolus	5.0 μg kg^{-1}	—
Infusion	3.0 μg kg^{-1} h^{-1}	—
Group 3		
Bolus	2.5 μg kg^{-1}	0.5 mg kg^{-1}
Infusion	1.5 μg kg^{-1} h^{-1}	0.1 mg kg^{-1} h^{-1}
Group 4		
Bolus	5.0 μg kg^{-1}	0.5 mg kg^{-1}
Infusion	3.0 μg kg^{-1} h^{-1}	0.1 mg kg^{-1} h^{-1}
Manual control		
Bolus	2.5 μg kg^{-1}	0.5 mg kg^{-1}
Infusion	1.5 μg kg^{-1} h^{-1}	0.1 mg kg^{-1} h^{-1}

Although not required to start control, the MAP response to a step change from 0% to 2% isoflurane inspired concentration was performed before surgery. This identified each patient's sensitivity to isoflurane and latency of response (the time taken from a change in isoflurane concentration to the first response of MAP). If the response indicated marked patient sensitivity, the maximum isoflurane concentration which the STC could use was limited to 3%.

A standardized programme was followed in each patient (fig. 1). Immediately after the start of surgery the control programme, run on the BBC in Basic, was started with the target pressure set at 50 mm Hg. The sampling time of the STC was set at 25 s, as previous experience had shown that the latency of response is within a range of 20–30 s. For the first five sample times, 2% isoflurane was given and then a low-gain proportional controller used for a further three sample times. The response of the MAP to the change in isoflurane concentration during these initial eight sample times allows an early estimation of each patient's characteristics; using this, the STC begins regulation at the ninth sample time: the error between the actual and desired MAP is

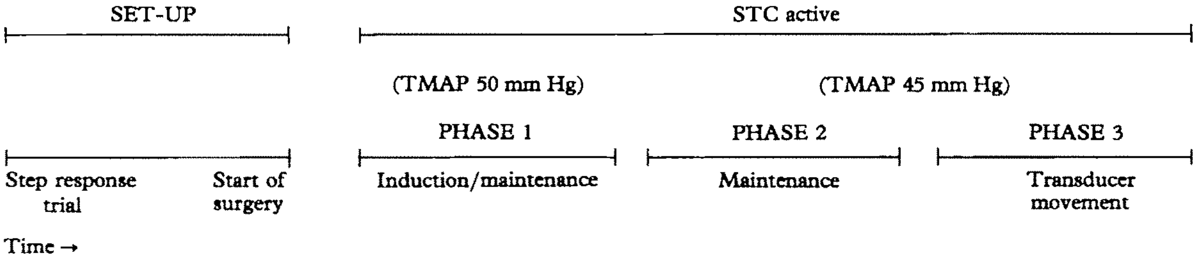

FIG. 1. Trial programme. TMAP = Target mean arterial pressure.

measured and the STC calculates the inspired isoflurane concentration required to decrease the MAP to the desired pressure within 75 s (three sample times); the isoflurane concentration required is updated every time interval; the relationship between the isoflurane concentration and MAP is used to modify the STC estimate of each patient's characteristics. (A fuller explanation of the control theory used, with mathematical proof, has been published previously [8].) The induction period was from the start of control until an MAP of 55 mm Hg was achieved, the phase 1 maintenance period continued until at least 10 min of stable control (50 ± 2 mm Hg) was obtained. The target pressure was then decreased to 45 mm Hg and the phase two maintenance period continued until there had been a further 10 min of good control (45 ± 2 mm Hg). Phase 3 started with the movement of the transducer upwards by 13.6 cm, inducing an offset of −10 mm Hg to the MAP which tested the transient response and stability of the STC. After the response of the controller to this simulated acute hypotension had restored the apparent MAP to 45 mm Hg (real 55 mm Hg) and, in the presence of a stable MAP, the transducer was returned to its original position, thus mimicking an acute increase in MAP requiring a further controller response to restore MAP to the target pressure. The MAP was then maintained at a true 45 mm Hg until the end of surgery when the STC was stopped.

The manual control group was treated the same as group 3 and one anaesthetist (C.R.M.) induced hypotension. The standard programme was followed, with the trend recording of the MAP and vaporizer output hidden, to avoid any historical assistance in determining the isoflurane concentration required to induce the correct hypotension.

To ensure patient safety, the anaesthetist could manually override the STC should an excessive undershoot of MAP, significant cardiac arrhythmia or controller instability warrant it. Any patient was excluded from the trial when the induction phase was longer than 15 min, additional labetalol given and the MAP reduced to 45 mm Hg, this pressure being accepted in our clinical practice. The MAP, ECG, target pressure and potentiometer position (isoflurane output) were recorded on disc and four-channel tape recorder. A chart recording of the MAP and potentiometer position was made also.

The effectiveness of the automatic and manual control was analysed by comparing the time spent within the ±5 and ±10-mm Hg control bands of each phase. After the induction phase was finished, the regulation of the actual MAP to the target MAP was assessed using the mean absolute error (MAE): the error is measured at each 25-s sample point and the quality of control is inversely proportional to the MAE. To compare the automatic with the manual control groups, non-parametric analysis by Kruskal–Wallis and Dunn's multiple comparison *t* test was used to compensate for the error of multiple *t* tests, skewed distributions and non-homogeneous inter-group variances [10, 11]. However, the data were sufficiently close to being normally distributed that ANOVA and Dunnett's *t* (for multiple comparisons) *P* values are given.

RESULTS

The four automatic and one manual control groups were similar for age, weight, sex and type of surgical procedure (table II). The STC provided accurate, reproducible and stable hypotension under the conditions tested (fig. 2). No patient was withdrawn from the trial because of

TABLE II. *Demographic data (mean (SD)) LF = Low-dose fentanyl; HF = high-dose fentanyl; L = labetalol*

	Manual control (LF+L)	Self-tuning closed-loop controller Group 1 (LF)	Group 2 (HF)	Group 3 (LF+L)	Group 4 (HF+L)
Age (yr)	30 (11)	25 (9)	32 (12)	33 (11)	32 (11)
Weight (kg)	74 (17)	71 (23)	73 (10)	70 (7)	74 (15)
(range)	(44–90)	(47–120)	(51–86)	(61–81)	(60–95)
Operation (Nasal/Ear)	5/3	5/3	4/3	3/5	5/4
Sex (M/F)	5/3	4/4	6/1	7/1	6/3

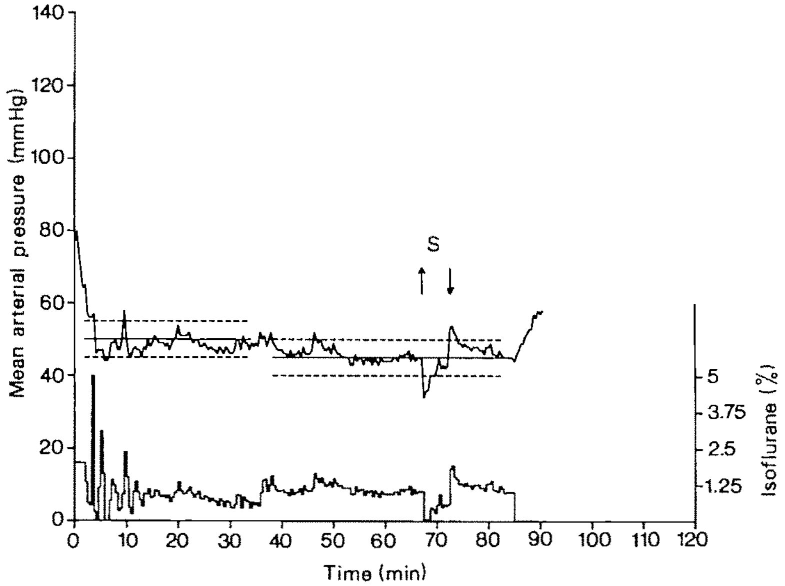

FIG. 2. Example of automatic control and the programme of MAP changes followed in a patient allocated to group 3 undergoing a tympanectomy. Initial control to the 50 mm Hg target pressure (——) is followed by a period at 45 mm Hg. Two perturbations in MAP, mimicked by transducer shifts, result in changes in the isoflurane inspired concentrations to regain regulation. The controller is switched off at the end of surgery to allow the MAP to return towards normal. Overall isoflurane requirement is low. S = Transducer shifts. ---- = ±5 mm Hg control band.

controller instability, inappropriate action or prolonged MAP offset, and the manual override facility was not used. One patient (who received high-dose fentanyl) was withdrawn because hypotension (MAP < 55 mm Hg) could not be induced with 5 % isoflurane within 15 min of phase I. The addition of labetalol increased this patient's sensitivity to isoflurane and effective automatic control was then obtained. Three patients (groups 3 and 4) showed a marked sensitivity to isoflurane and the inspired maximum concentration was limited to 3 %.

The mean observed time delay before the start of the MAP response to a change in isoflurane concentration for the 42 patients studied was 24.2 (SD 2.6) s (range 18–30 s) and did not vary with time. The quality of STC control obtained was compared with the manual control. The duration of control was similar for all groups (table III). The starting MAP was greater in low-dose fentanyl groups and the induction phase of hypotension was prolonged in both low- and high-dose fentanyl groups (Kruskall–Wallis $P < 0.005$). The extent to which the reduction in arterial pressure was greater than intended (undershoot), the duration with MAP within ±5 or ±10 mm Hg of the target pressure, and the SD of MAP did not differ between treatment groups. MAE, measured at each 25-s sample point, were similar for the three control phases, both assessments indicating there was no difference in the quality of control obtained.

The isoflurane requirement to maintain hypotension reflected the different background anaesthetics, groups which did not receive labetalol needing greater inspired concentrations than the control group (table III: phase 2 isoflurane).

Problems encountered with STC

In three patients, electrical interference (e.g. diathermy) via the transducer head falsely increased MAP during the induction phase of hypotension. The ensuing distortion of the relationship between the inspired isoflurane concentration and MAP before the STC could assess accurately the patient's characteristics caused a bias, resulting in impaired regulation. By restarting the estimator, an accurate assessment was achieved with subsequent good control, further diathermy activity causing negligible effect on the overall regulation.

Excessive controller action with oscillation of

TABLE III. *Regulation performance (mean (SEM)). An = ANOVA; KW = Kruskal–Wallis.* *P < *0.05;* P < *0.01 (Dunnett's* t *test)*

	Manual control (LF+L)	Self-tuning closed-loop controller Group 1 (LF)	Group 2 (HF)	Group 3 (LF+L)	Group 4 (HF+L)	Comparison
n	8	8	7	8	9	
Duration (min)	77 (6.6)	82 (7.3)	97 (14.4)	75 (5.7)	82 (7.8)	An: ns KW: ns
Starting MAP (mm Hg)	81 (4.7)	95 (3.3)*	87 (3.4)	87 (4.2)	74 (3.1)	An: $P < 0.005$ KW: $P < 0.05$
Time to 55 mm Hg (min)	4.0 (0.5)	9.3 (1.6)**	7.9 (1.0)*	6.4 (1.0)	2.6 (0.3)	An: $P < 0.001$ KW: $P < 0.005$
Undershoot (mm Hg)	3.3 (0.8)	4.5 (1.3)	2.8 (0.5)	4.1 (0.4)	3.6 (1.0)	An: ns KW: ns
Time at target ±5 mm Hg (%)	90 (1.8)	83 (3.4)	88 (3.1)	89 (2.2)	84 (4)	An: ns KW: ns
Time at target ±10 mm Hg (%)	99 (0.5)	96 (0.9)	96 (1.9)	98 (0.6)	95 (1.8)	An: ns KW: ns
SD for complete run	3.4 (0.3)	4.4 (0.5)	4.2 (0.7)	3.5 (0.3)	4.4 (0.6)	An: ns KW: ns
Mean Absolute Error from target MAP						
Phase 1 50 mm Hg	2.6 (0.4)	3.3 (0.5)	2.2 (0.2)	2.2 (0.2)	3.0 (0.4)	An: ns KW: ns
Phase 2 45 mm Hg	1.7 (0.2)	1.9 (0.4)	2.4 (0.4)	1.4 (0.2)	2.2 (0.5)	An: ns KW: ns
Phase 3 Shift to end	3.5 (0.5)	4.0 (0.6)	3.3 (0.3)	3.9 (0.7)	4.1 (0.5)	An: ns KW: ns
Phase 2 isoflurane (%)	1.8 (0.2)	3.7 (0.4)**	3.0 (0.4)*	1.9 (0.3)	1.0 (0.2)	An: $P < 0.001$ KW: $P < 0.001$

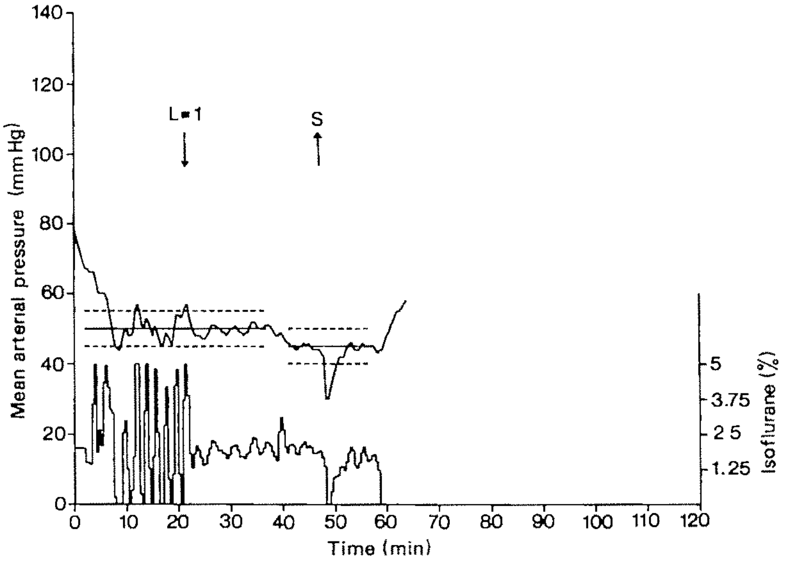

FIG. 3. Onset of oscillatory control is stabilized by introducing a damping factor of L = 1. Only one transducer shift (S) was performed in this patient (group 3, septorhinoplasty). —— Target pressure; ---- ±5 mm Hg control band.

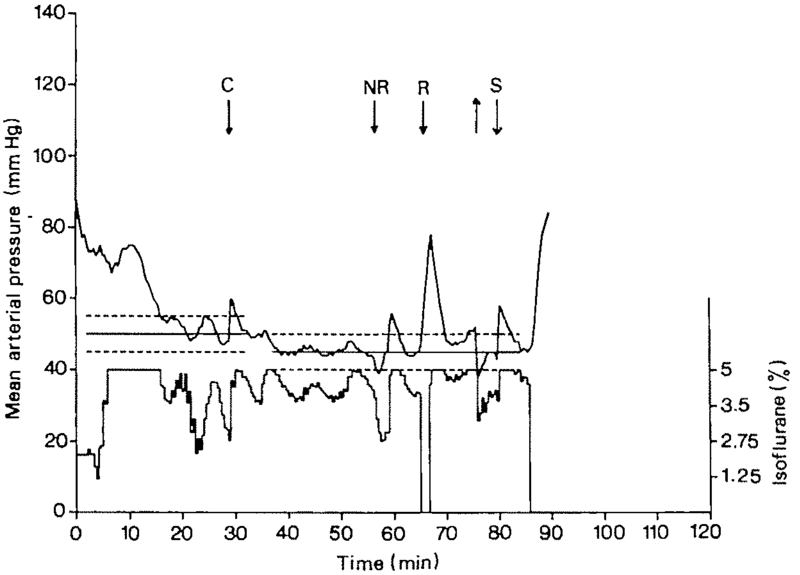

FIG. 4. Example of the multiple problems that may affect MAP control. Surgical stimulus (chiselling: C), nodal rhythm (NR), vaporizer refill (R) and transducer shifts (S) perturbing arterial pressure (group 1, septorhinoplasty). —— Target pressure; ---- ±5 mm Hg control band.

the isoflurane concentration between 0 % and 5 % occurred because of inadequate identification of a patient's response, and is illustrated in figure 3. The sympathetic oscillation in MAP caused by the controller overactivity was decreased by changing the controller damping factor (L) from 0, the usual value, to 1 [8]. This reduced the rate of response of the controller to a more appropriate value for this patient, resulting in effective regulation, but still with a rapid response to any perturbation in pressure. Oscillation in the isoflurane concentration developed in seven patients, and damping was used to smooth the control action, but in only three of these subjects was there a discernible effect on MAP.

The high isoflurane requirement in the low-dose fentanyl group limited the effectiveness of isoflurane for hypotension as the STC required inspired concentrations greater than 5 % (fig. 4). In this example the induction phase was prolonged despite the selection of 5 % isoflurane and, although the increases in MAP produced by surgical stimuli (nasal chiselling) and change in target pressure were well regulated, the availability of a higher isoflurane concentration would have enabled more rapid control. The onset of a transitory nodal rhythm (NR) caused the MAP to decrease suddenly and the STC responded correctly by reduction of the inspired isoflurane concentration. The restoration of sinus rhythm increased MAP, and again the STC responded correctly to limit the potential change in MAP. The refill of the vaporizer interrupted the regulation, resulting in the rapid increase in MAP which is shown. The difficulty in regaining control is evident by the offset in MAP, even with the selection of 5 % isoflurane.

DISCUSSION

Automatic controllers have been developed for the regulation of MAP [2–5, 7–9], neuromuscular block [12], depth of anaesthesia [13] and alveolar concentration of inhalation agents [14]. Many of these control systems are PID algorithms, based on the work of Sheppard [2] and the modifications of Slate [5]. PID controllers are limited by their sensitivity to the response of individual patients [5, 15]. The variation in intra- and inter-patient drug sensitivity, differences in response latency (possibly time-varying), and alterations in surgical stimulation may cause instability in these controllers if the patient's characteristics are outside the range accommodated in their design. The reduction in MAP, particularly with induced hypotension, may activate autoregulatory systems in an attempt to restore MAP toward a normal value [16, 17]. These responses increase the likelihood of instability or the failure of control by altering patient sensitivities.

To obtain stable regulation in a large patient population, the gain (change in drug dose per unit change in MAP) of a PID system is preset to a low level at start-up [5]. This produces a cautious controller with a slow and well-damped response to changes in MAP, particularly in patients who are resistant to the hypotensive drug used. Adaptive, self-tuning controllers are able to change their gain characteristics in response to the initial changes in MAP and to any time-related variation in each patient [15, 18]. By offering the best compromise between controller stability and transient response, adaptive controllers are theoretically capable of achieving better regulation. The generalized minimum-variance control algorithm used in this study is based on the theory of Clarke and Gawthrop [6], a comprehensive appraisal of which has been reported previously [8, 18].

The quality of MAP regulation is good when the error between actual and desired MAP is small, and when control of MAP is achieved rapidly after the start of hypotension or an acute perturbation in MAP. The study tested the controller under clinical conditions by demanding the induction of hypotension, a change in target pressure and the need to respond to acute alterations in arterial pressure. Previous studies in animals have injected i.v. bolus doses of SNP or adrenaline to mimic haemorrhage and increases in sympathetic activity, respectively [3, 4], but the associated hazards make this unacceptable in a clinical setting. The transducer movements used in this study produced an apparent pressure change which required controller action, but without acute increases in myocardial contractility and irritability, or in organ perfusion pressure.

The quality of regulation produced by the STC during the four background anaesthetics has been compared against that obtained during manual control. The anaesthetist's performance was equalled by the STC in all four groups whether assessed by the time spent within the ±5 or ±10-mm Hg target pressure bands or by mean absolute error of MAP. Stern and colleagues compared an STC against a single anaesthetist [19]; both performed equally well, but each had the advantage of a learning period before the start of control, this being unavailable in the clinical situation. Smith and colleagues used a discrete digital controller to adjust either the inspired concentration of halothane or the infusion rate of SNP for regulation of AP [3]. The controller equalled or bettered the manual control produced by 11 anaesthetists. The characteristics of their animal model were well defined and the internal gains of the controller were predetermined to enhance the performance of the controller, an advantage not available in clinical practice. A system developed by Meline and co-workers combined PD and minimum-variance control to eliminate the need for a learning phase [20]. Accurate and rapid control was obtained in a study of 10 dogs and, in a subsequent comparison against 10 anaesthetists, no difference in the quality of control was found [4]. However, the PD algorithm assumes that the drug sensitivity is inversely proportional to the weight of the dog, which may be an incorrect assumption, and an undershoot or offsets from the target pressure could occur. As the stability of the minimum-variance part is sensitive to choice of sampling time, this control design would seem of limited value for clinical use. The STC reported in this paper did not require a learning period, did not require that the patient characteristics be defined precisely and, after the initial eight sample times (3.3 min), used only the generalized minimum-variance controller. Its performance in clinical use during surgery with the associated background noise matches that of the above controllers tested under laboratory conditions.

Some of the requirements for a hypotensive drug in a control system are that it should: be easy to adjust the rate of administration; preferentially decrease systemic vascular resistance and maintain cardiac output; have a short half-life (i.v. drug) or low blood/gas partition coefficient (inhalation drug) for a minimal delay in patient response to changes in rate of administration. Most publications of automatic MAP control have used SNP as the vasoactive drug [2–5, 7–9, 19, 10], but isoflurane has potential advantages and few disadvantages.

(1) Isoflurane fulfils the physical criteria for automatic control [21], and has a cardiovascular profile [22–24] and effect on organ perfusion similar to those of SNP during hypotension [25]. It has the advantage of minimal metabolism [26] and it decreases the activity of autoregulatory mechanisms such as the baroreceptor reflex [27], whilst SNP may enhance the activity [28].

(2) An increase in MAP, possibly as a result of surgical stimulation, results in an increase in the inspired isoflurane concentration and therefore of anaesthetic effect. This is a fortuitous side-effect of using isoflurane as the hypotensive agent, rather than an attempt to match the anaesthetic dose to the level of stimulation.

(3) The property of isoflurane to decrease cerebral metabolic rate and maintain cerebral blood flow [29], without inducing intracerebral shunting [30], has a beneficial effect on the cerebral oxygen supply/demand balance. Higher cerebral tissue oxygen pressures during isoflurane hypotension [31] and lower critical cerebral blood flows during carotid endarterectomy with isoflurane anaesthesia [32] suggest that this drug may offer a degree of cerebral protection if hypoperfusion should occur during hypotension.

(4) Isoflurane has been shown to cause coronary steal in humans and animal models [33]; the high concentrations needed to obtain MAP regulation in some groups in this study may increase the risk of myocardial ischaemia [34]. However, induced hypotension is not recommended in patients with coronary artery disease. No evidence of myocardial ischaemia was observed on the ECG monitor during the control runs or on subsequent review of the tape recordings. SNP also has been associated with the coronary steal phenomenon and is therefore not a viable alternative [33].

We conclude that, under clinical conditions and varied anaesthetic backgrounds, the STC provided safe, effective regulation of arterial pressure, with a performance equal to that of manual control.

ACKNOWLEDGEMENTS

This study was supported in part by Ohio Medical Associates (Anaquest), South Western Regional Health Authority locally organized scheme No. 158 and by Bristol and Weston Health Authority District Medical Research Project No. 427.

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Br. J. Anaesth. (1989), **63**, 31–35

AUTOMATIC CONTROL OF NEUROMUSCULAR BLOCK WITH ATRACURIUM

A. D. MacLEOD, A. J. ASBURY, W. M. GRAY AND D. A. LINKENS

SUMMARY

We have developed and tested a system for providing automatic control of neuromuscular block with atracurium. The degree of neuromuscular block was monitored in the small muscles of the hand using a Datex Relaxograph, and the signal was used as the controlled variable for a proportional plus integral controller. A preloaded integral was used to shorten the period of stabilization. The system was tested in 36 patients undergoing surgery and found to produce stable block. For a target T1 of 20% of control value, the mean block was 18.7 (SD 1.3)% of baseline T1 and the mean consumption of atracurium was 5.39 (SD 1.23) $\mu g\ kg^{-1}\ min^{-1}$. The block was sufficiently stable to act as a background for studies of pharmacological and physiological interactions with atracurium.

Steady neuromuscular block at a predetermined level is valuable during long operations; this may be difficult to achieve using a manually controlled infusion. Automatic control of neuromuscular block has been achieved in patients with drugs such as pancuronium and vecuronium [1–3]. Atracurium has a relatively short duration of action and non-hepatic elimination and is likely to be more amenable to automatic control than pancuronium and vecuronium [4,5].

Wait and co-workers [4] described a simple on–off control system which, despite being intrinsically oscillatory, performed well and produced a mean maximum deviation above the target T1 of 3% in 11 patients. (T1 is the Relaxograph ratio of electromyograph (EMG) after block to that before the block). Webster and Cohen [5] described a portable control system incorporating proportional and derivative terms, which produced a mean T1 of 8.9% for a target of 10% in 20 patients.

The object of this study was to devise a simple, robust control system capable of controlling block to a predetermined level and able to work within the time constraints of a routine session. This requires rapid achievement of the target level, as surgeons invariably require adequate paralysis early in the operation. We have also quantified the stability of the system in order to assess the extent of control.

PATIENTS AND METHODS

After local Ethics Committee approval, we studied 36 patients (29 female) in ASA categories I or II presenting for elective general surgery. We excluded patients with known sensitivity to anaesthetic drugs or myoneural disorders and patients taking drugs known to affect neuromuscular transmission.

Anaesthetic technique

The patients were premedicated with temazepam by mouth 90 min before surgery. In the anaesthetic room the Relaxograph electrodes were applied at the wrist, which was immobilized in a light splint. After insertion of a cannula into an appropriate vein, the lungs were preoxygenated and anaesthesia was induced with thiopentone 3–5 mg kg^{-1}. Baseline EMG recordings were obtained and atracurium 0.25 mg kg^{-1} administered i.v.;

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the trachea was intubated when T1 reached 25% of the baseline value. The lungs were then inflated with 67% nitrous oxide and 1% enflurane in oxygen and the patient was moved into the operating room and connected to an automatic ventilator delivering the same gas mixture. The automatically controlled infusion was started when T1 from the initial bolus had increased to 15% of the baseline value.

During surgery, enflurane anaesthesia was supplemented with boluses of fentanyl as indicated clinically. In addition to normal clinical signs, ECG and arterial pressure were monitored, and i.v. fluids were given as appropriate. At the end of surgery, residual block was antagonized with neostigmine and atropine. The level of block was monitored until the patient moved spontaneously, making further EMG recordings unreliable.

Equipment

The level of neuromuscular block was monitored using a Datex Relaxograph neuromuscular transmission monitor [6], which records an evoked EMG in the small muscles of the hypothenar eminence every 20 s. The Relaxograph rectifies and integrates the evoked EMG and calculates the ratio of the result during block to that before. This ratio is termed T1.

The Relaxograph was connected via its serial interface to a Research Machines 380Z-D microcomputer, which was in turn connected to a modified Vickers IP3 pump loaded with a syringe containing atracurium 500 $\mu g\ ml^{-1}$ in saline. The syringe was connected to the dedicated cannula sited in a peripheral vein, thereby completing the control loop.

The computer calculated the dose of atracurium at 20-s intervals using the following proportional-plus-integral (PI) algorithm:

$$\text{Output of atracurium (ml h}^{-1}) = K_p e + K_i(\textstyle\sum e + P)$$

where e = difference between the actual T1 and the target T1; K_p and K_i = proportional and integral gains; P = preloaded value for the integral, which is included to shorten the stabilization time. The target T1 was always 20%. K_p was set at 0.02 × weight (kg) and K_i at 0.0007 × weight (kg); these values were calculated on the basis of four preliminary trials in which a steady infusion was administered until stable block was achieved and the infusion rate was reduced suddenly by 25%. The response of the T1 to this step change in input was analysed to give appropriate values for the proportional and integral gains using the empirical rules described by Ziegler and Nichols [7]. The values of K_p/weight and K_i/weight quoted above were the mean values obtained from these trials. Ideally, the value of P would be such that the infusion rate would be sufficient to maintain steady block with zero value for e, that is with no proportional component in the control signal. On the basis of data previously published [8], P was initially set to 680. After the first three patients it was changed to 1000, which represented the mean dose required to maintain steady block at 20% in the three patients (see Results).

The computer was programmed to print all the data received from the Relaxograph and the corresponding settings sent to the syringe pump. This information was stored also on floppy discs.

Analysis of data

As we were interested mainly in studying the behaviour of the system during the period of steady neuromuscular block, we required an operational definition of the "stable period". The start of this period was defined in two ways, depending on whether or not there was an overshoot above target after starting automatic control. If there was, the beginning of the stable period was the time at which T1 returned to 20% after the overshoot. If there was no overshoot the stable period began when T1 first started to decline after the controller had been started. The stable period ended when surgery finished. (For one patient, a different criterion was used, as described in the Results.) Figure 1 illustrates these definitions of the stable period.

We measured the extent of control by two indices: the root mean square deviation (RMSD) of the stable period points about the target block level (20% of the control EMG); and the point count (PC), which is the number of stable period points above the target expressed as a percentage of all the stable period points. The RMSD gives an index of the extent of spread of values about the target, irrespective of whether they were above or below the target, while the PC indicates if the block achieved tended to lie above or below the target. The consumption of atracurium was calculated as the mean dose rate over the stable period.

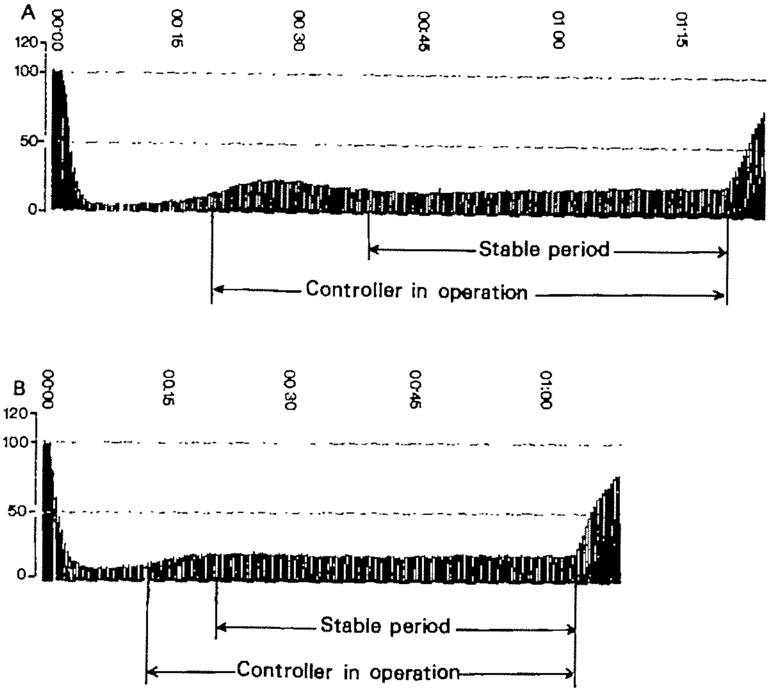

FIG. 1. Relaxograph traces from two patients, illustrating how the start of the stable period was defined. A: In a patient in whom there was an initial overshoot of the target T1. B: In a patient in whom there was no initial overshoot. For patient A RMSD was 2.5%, PC was 4% and SD was 1.5%, for patient B RMSD was 1.0%, PC was 34% and SD was 0.8%.

RESULTS

Details of the patients studied are presented in table I. The operations were mastectomies (23), major arterial surgery (six), and eye and general surgery (seven).

The degree of neuromuscular block obtained was clinically satisfactory in all patients, with one exception, in whom the surgeon reported that the abdominal muscles were "tight" on closure, although there had been no previous indication of unsatisfactory relaxation. The system proved easy to manage by a single-handed anaesthetist (A.MacL.) without delaying a busy operating list.

Results of the automatic control procedure are presented in table I, and representative Relaxograph traces from two patients are shown in figure 1. The initial atracurium bolus generally caused T1 to decrease to approximately 10%, although in two patients T1 decreased to 2%. After the start of automatic control in each of the first three patients, T1 displayed a considerable overshoot of the 20% target before it began to decline (maximum T1 were 28, 23 and 26% for patients Nos 1, 2 and 3, respectively). In an attempt to minimize this problem and the associated potential for patient movement, the value of the integral preload was increased from 680 to 1000 after these three patients had been studied.

In all patients except one, the end of the stable period was taken as the time when surgery

TABLE I. *Summary of patient data (n = 36) and results of automatic control procedure. RMSD = Root mean square deviation; PC = point count*

	Mean	SD	Range
Age (yr)	62.5	10.3	39–78
Weight (kg)	61.9	13.0	40–99
Duration of stable period (min)	43.9	16.3	21–77
Mean T1 (%)	18.7	1.3	16.3–21.7
SD of T1 (%)	1.47	0.69	0.6–3.6
RMSD (%)	2.21	1.01	0.8–4.4
PC (%)	25.2	21.7	0–81
Dose ($\mu g\ kg^{-1}\ min^{-1}$)	5.39	1.23	2.7–8.6

finished. The one exception was patient No. 6, who had an aortic bifurcation graft, for whom the stable period was considered to end when the aortic cross-clamp was applied. It was felt that application of the cross-clamp could lead to alteration in the volume of distribution and possibly produce transient instability in the control system. However, there was little alteration in the degree of block after the cross-clamp was applied.

There was an overshoot at the beginning of the stable period in 23 patients. The highest peak T1 obtained in any patient was 29 %. In those patients in whom there was overshoot, the mean peak value of T1 was 23.7 (SD 2.4) %. The mean time from controller implementation until the beginning of the stable period was 11.0 (SD 9.1) min.

There was no significant correlation ($P < 0.05$) between age and dose of atracurium.

DISCUSSION

This work differs from previous studies in this area in the following ways. First, we have used a proportional plus integral system with a preloaded integral, in contrast with Wait and co-workers [4] who used a simple on–off system, and with Webster and Cohen [5] who used a proportional plus derivative system. The integral term is a standard control system strategy for removing steady state error [9], and we found such an error in preliminary trials without an integral term. The second innovation in our study is the quantification of the quality of control. This was achieved by means of the point count and the root mean square deviation; the use of such measures in future studies may allow comparison of different control strategies.

T1 20 % of baseline proved clinically satisfactory in all patients, with one exception. The 20 % target was chosen because we felt that it would provide satisfactory block, and because the working point would be on the linear region of the atracurium dose–response curve. Selecting a considerably lower target, say 10 %, would lead to the possibility of the working point moving outside the linear region of the dose–response curve, where the use of a PI controller would be inappropriate. It may be that aiming for a target T1 of 15 % would eliminate the occasional difficulty which might arise with a target of 20 %.

The time that elapsed between the start of automatic control and the beginning of the stable period (mean 11.0 (SD 9.1) min) did not delay the start of surgery or cause other clinical problems.

The value of 1.47 % for the mean standard deviation of T1 indicates that, in general, a steady level of block was obtained. The closeness of the mean RMSD to the mean SD (2.21 % compared with 1.47 %) indicates that the degree of block achieved was generally close to the target. As the overall mean T1 (18.7 %) and the mean PC (25.2 %) show, the trend was for the individual mean T1 to be slightly less than 20 %. This probably may be explained by definition of the stable period. In those patients in whom there was an initial overshoot, the controlled period began when the T1 returned to 20 % and at this point there was a downward trend in the value of T1. In the remainder of the patients (those in whom there was no overshoot), the stable period began at a value less than 20 %. As a consequence the initial part of each stable period started with a series of T1 values below target. Therefore, some time elapsed from the beginning of each stable period before the T1 returned to 20 % and it was probably the contribution of this initial portion that led to the overall mean T1 being less than target.

In general, the effect of the starting bolus gave a good indication of the subsequent behaviour of the patient. Those patients in whom the bolus caused the greatest decrease in T1 tended to be those who required the lowest infusion rates to maintain T1 at target and those on whom the bolus dose had the least effect tended to require a higher infusion rate.

The mean dose is at the lower end of the range recommended by the manufacturers for atracurium. This is not surprising, for three reasons. First, the use of enflurane potentiates the effect of atracurium [10]; second, constant infusion is probably a more efficient way of using atracurium than bolus injections; third, the manufacturer's recommended range is probably biased towards those patients who are least responsive to atracurium.

We found a considerable range in the atracurium dose required to maintain steady block, in agreement with other workers [11]. However, the three-fold variation found in this study is smaller than that for other myoneural blockers. D'Hollander and colleagues [12] used vecuronium in 20 ASA I and II patients and found a 10-fold variation in the range of dose required to maintain 10 % twitch tension. Part of this difference may be explained by the fact that, in contrast with other relaxant drugs, there is no decrease in atracurium requirement in the elderly; this has been demonstrated in a previous study [13] and is supported by the lack of a significant correlation between age and dose of atracurium in this study. This relatively small range of atracurium requirement suggests that a simple control system such as this, in which no self-tuning occurs, should work better with atracurium than with other agents. Those patients who were particularly resistant to block would demonstrate a marked overshoot at the start of the control, while those who were especially sensitive would suffer a large initial depression of T1. In both groups there would be a considerable delay before the onset of the stable period, even if overt instability did not occur. It is possible that there are some patients whom our system would not control (those at each end of the range of sensitivity), but adequate control was obtained for a patient whose requirement was 50% of the mean and for another whose requirement was more than 50% greater than the mean.

The standard method of administering neuromuscular blocking drugs is to give an initial bolus followed by subsequent boluses of approximately 33% of the initial dose. The replacement of these subsequent boluses by a continuous infusion under automatic control has the following advantages: there are no periods of serious over- or under-dosage; prompt antagonism can be achieved readily if surgery finishes unexpectedly early; and atracurium is used efficiently.

ACKNOWLEDGEMENT

A.D.M. was supported by The Wellcome Foundation Ltd during the course of this work.

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Br. J. Anaesth. (1989), **63**, 36–43

COMPUTERIZED MONITORING OF DEPTH OF ANAESTHESIA WITH ISOFLURANE

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SUMMARY

Changes in brain activity were studied at different depths of isoflurane anaesthesia. Ten healthy women (ASA group I) were investigated during non-critical surgery. Two channels of the EEG were stored on tape simultaneously with alveolar concentration of carbon dioxide, inspired oxygen concentration, mean arterial pressure, ECG and temperature. Signal processing was made off-line. Spectral information from 2-s EEG segments was extracted using autoregressive modelling. Repetitive hierarchical clustering was used to define a common learning set of basic patterns. With this learning set, the EEG was classified, and the results presented in a class probability histogram. The basic patterns were related to the clinical depth of anaesthesia in all patients and assigned specific colours. Using this colour code, the class probability histogram showed a high degree of simplicity. Decreasing or increasing the isoflurane concentration caused the same trend in the class profile in all patients. This indicates that the EEG pattern might be a sensitive tool for decision making during administration of general anaesthetics.

Monitoring of brain activity during surgery has been used mainly to assess cerebral activity during carotid endarterectomy and extracorporal circulation [1–5]. Another objective has been to correlate changes in brain activity with depth of anaesthesia. These investigations include both volatile and i.v. anaesthetic agents [4,6,7].

The aim of the present study was to investigate the changes in the electroencephalogram (EEG) during changes in depth of anaesthesia.

A computer-based system was used off-line for signal analysis of the EEG and for visualizing and recording the EEG pattern and physiological variables monitored traditionally during anaesthesia.

Special attention was payed to the design of the screen display, as pattern recognition of simultaneous changes in EEG and other physiological variables may, in future on-line use, serve to help the anaesthetist to make decisions.

Visual inspection of the EEG strip chart recording is time consuming and requires the presence of an experienced neurophysiologist. Computer-based signal processing methods are useful [1–9] and have been used during surgery when brain metabolism was at risk; it was observed that extensive monitoring improved the neurological outcome for the patient [5,7].

The automatic methods use spectral analysis by means of Fast Fourier Transform (FFT) and period/amplitude analysis. The amplitude spectra obtained by the FFT have been displayed as compressed spectral array (CSA) plots [10,11], or as density spectral array (DSA) plots [12]. Hitherto, EEG has not been useful clinically for monitoring depth of anaesthesia because the changes were agent specific and dependent on the critical state of the patient [13]. To overcome this problem, only patients belonging to ASA group I were selected and the same anaesthetic agent was used in all patients.

MATERIALS AND METHODS

We studied 10 healthy women (aged 25–45 yr, ASA I, body weight not exceeding 10 % of ideal) undergoing simple hysterectomy. There was no

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history of previous neurological disorder and tranquillizers and analgesics were not administered routinely for several weeks before operation. The day before operation, informed consent was obtained. The investigation was approved by the local Ethics Committee.

Anaesthesia was induced with thiopentone 5 mg/kg body weight and, before tracheal intubation, a priming dose of gallamine, and suxamethonium 100 mg were administered. After intubation, anaesthesia was maintained with 1.0–2.5 % isoflurane and 66 % nitrous oxide in oxygen. Relaxation was maintained with gallamine and the lungs were ventilated mechanically by a Dameca MC 801 anaesthetic ventilator connected to a circle system with carbon dioxide absorption. The duration of anaesthesia was 50–150 min and the temperature was constant (±0.7 °C).

Monitoring of EEG from both hemispheres (P_3-Fp_1 and P_4-Fp_2) was started before induction of anaesthesia. In addition, the traditional physiological variables, ECG, heart rate and temperature, were recorded. End-tidal (alveolar) carbon dioxide concentration ($F\text{A}_{\text{CO}_2}$) and inspiratory oxygen concentration ($F\text{I}_{\text{O}_2}$) were measured breath to breath with a Datex Normocap CO_2 monitor. Mean arterial pressure (MAP) was recorded non-invasively by a Criticon Dinamap Vital Signs Monitor. All information was stored on a eight-channel Racal Store 8 frequency modulated magnetic tape recorder. Further analysis of signals was performed off-line.

According to the procedure, the initial isoflurane vaporizer setting was selected by the same experienced anaesthetist in all patients, corresponding to clinical signs indicating depth of anaesthesia adequate for surgical needs. The loading and maintenance concentration was guided individually by the clinical condition of the patient. From induction of anaesthesia the mechanical ventilator was adjusted to $F\text{A}_{\text{CO}_2}$ 5.0–5.5 vol %, corresponding to normoventilation.

Twenty-five to 30 min after start of surgery, when the clinical condition was considered stable, the isoflurane concentration was increased by approximately 50 % to study the EEG at a greater depth of anaesthesia. After 20 min maintenance concentration of isoflurane was re-established. Thirty minutes later, slight hyperventilation was induced, corresponding to $F\text{A}_{\text{CO}_2}$ 4.0–4.5 vol %; this was discontinued after 20 min.

After operation all anaesthetics were discontinued and the neuromoscular block was antagonized with neostigmine.

SIGNAL PROCESSING

The signals were analysed off-line in a laboratory using an Intel 310 computer system. The computer performs multi-tasking real-time programs, and is equipped with analog-to-digital converter (ADC: 12-bit resolution in eight channels) and a high-resolution colour graphic display system (1024 × 512 pixels and 256 programmable colours). Hard-copies of the displayed parameters were made on a Tektronix 4696 colour-graphic jet-ink printer. Clinical events were marked on the magnetic tape recorder during surgery and transferred to the computer system.

The EEG signals were filtered with a 25-Hz, fourth order anti-aliasing filter, sampled at 100 Hz and pre-emphasized digitally by a first order high-pass filter. The EEG was divided into 2-s segments. From each segment, 11 parameters representing the amplitude and spectral information of the EEG were extracted using auto regressive (AR) modelling [14–16]. The pattern recognition was performed using a probabilistic classifier (Bayes' decision theory [17]). The classifier used a learning set of patterns defined by hierarchical clustering analysis. This type of learning is often referred to as "unsupervised learning".

For this analysis we selected a set of approximately 1000 EEG segments representing typical EEG patterns from different stages of anaesthesia. During hierarchical clustering [17] the algorithm merged the two most likely segments into one, step by step, starting with the initial number of segments and ending with one. As in pattern recognition, the segments were characterized by 11 parameters derived by AR-modelling. The clustering analysis was represented graphically in a dendrogram (fig. 1A). By interactive inspection of nodes in the dendrogram, where the dissimilarity measure between patterns increased rapidly, a representative set of 10–15 classes could be defined (fig. 1B). These classes were used as learning set for the classification of EEG activity during on-line analysis.

During analysis the results were displayed on the graphic screen. The last 1 h of anaesthesia was shown, but the whole period was stored for later inspection and production of hard copies for the

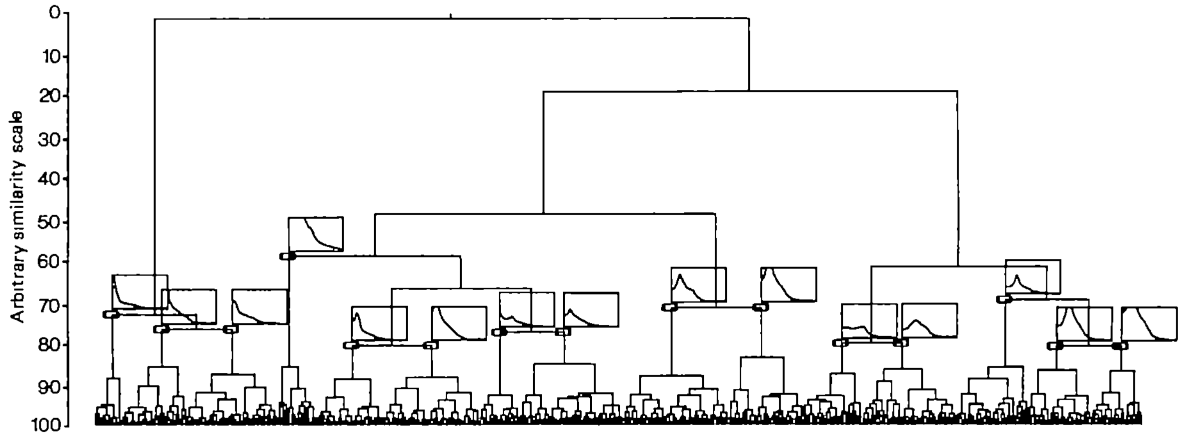


Figure 1 A

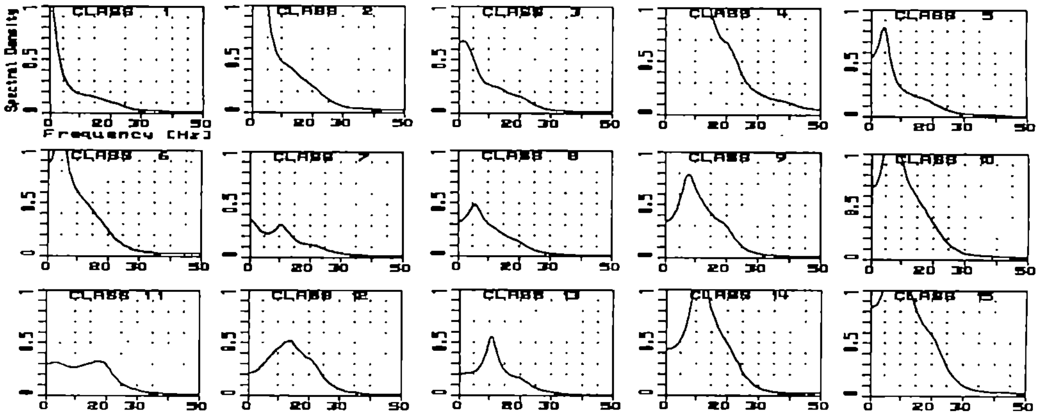


Figure 1 B

FIG. 1. A: Example of a dendrogram—a graphic description of the result from hierarchical clustering. The bottom level (level 1) in the dendrogram shows all segments as singleton clusters. At any level, after level 1, two clusters are merged to form a new cluster, and they stay together at all subsequent levels. The dendrogram is drawn to a similarity scale (ordinate) to show the similarity between the two clusters that are merged. This particular dendrogram is based on data from all patients in the group anaesthetized with isoflurane. The small amplitude spectra represent mean values for the marked subtrees. B: Enlarged set of mean spectra for the nodes marked in A. Abscissae: 0–50 Hz; ordinates arbitrary amplitude scale (spectral density) (range 0–1). All spectra are drawn to the same scale, comparable with respect to amplitude. A parametric description of this set of basic patterns acts as a common learning set for classification of EEG activity during surgery—common for all patients anaesthetized with isoflurane.

patient record. The parameters from the EEG analysis were displayed as a function of time:

(a) as Colour Density Spectral Array plots, where each plot (line) represents the amplitude spectrum for the most frequently occurring EEG pattern during a 10-s period;

(b) as a class probability histogram, where each plot (line) represents the relative occurrence of any class in percent—the class profile;

(c) as the symmetry between hemispheres.

In addition, the trend curves for $F\mathrm{I}_{\mathrm{O}_2}$, $F\mathrm{A}_{\mathrm{CO}_2}$, MAP and heart rate were displayed. In this way the correlation between EEG and the traditionally monitored physiological variables could be studied by pattern recognition.

A colour-graphic hard copy could be printed on-line during signal processing or off-line after the analysis had been performed. Changes in depth of anaesthesia and surgical procedure were marked on the print.

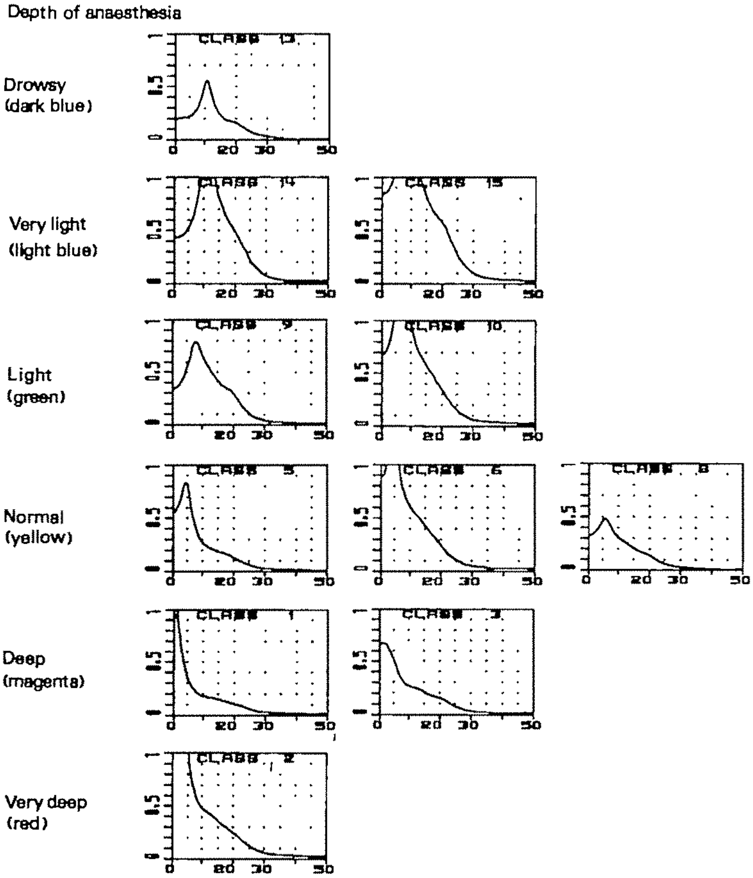


FIG. 2. The set of basic EEG patterns correlated to depth of anaesthesia and colour coded in order to give the anaesthetist support in his decision making.

A *common* learning set of EEG patterns representing isoflurane anaesthesia was obtained using "linked" clustering analysis: from the clustering sequences of the 10 individual patients we selected a step, where 50 different clusters were represented. By linking the 50 clusters from the 10 patients, we gathered 500 EEG patterns representing a typical *common* EEG sequence.

After a new hierarchical clustering analysis, we obtained a common set of classes (fig. 1B), which could be used for all patients anaesthetized with isoflurane. The dominant feature in the common learning set was the peak frequency and the configuration of the spectrum.

RESULTS

In all patients the class probability histogram generated from the common learning set was related to the clinical events during anaesthesia. The classes found during light, medium and deep levels of anaesthesia were tabulated. From this table a set of classes of frequency and amplitude patterns related monotonically to the depth of anaesthesia were extracted and assigned colours (fig. 2).

A peak frequency of 10–12 Hz was found during light anaesthesia (blue and green). At medium anaesthesia the peak frequency shifted to 5–7 Hz (yellow), and a small peak was detected in the 15–20 Hz range. During deep anaesthesia the peak was found in the very low frequency band, 1–5 Hz (magenta and red).

Figure 3 shows a black-and-white representation of a typical hard copy from the isoflurane series. Major events were marked to the left. Events of special interest are: induction with thiopentone (T): 20 min hyperventilation (between ↑ and –); 20 min increased anaesthetic concentration (from 1.5 to 2.5 vol %) (between > and <); decreasing anaesthetic concentration from 1.5 to 1.0 vol % (second <) and again from 1.0 to 0.5 vol % (third <).

Induction with thiopentone (T) caused a short presence of very low frequency, high amplitude activity, hardly noticeable in the hard copy because of low time resolution. Isoflurane was administered at x. The depth of anaesthesia increased gradually, and after 1 h the class probability histogram (central record) was dominated by the yellow classes (white areas in figure 3) as assigned to medium anaesthesia.

At >, the isoflurane vaporizer setting was increased by 50 %. This change was immediately reflected in the class histogram, which was now dominated by the magenta-plus-red classes (black in figure 3: area B) assigned to deep levels of anaesthesia. When maintenance concentration was re-established (<), the yellow class reappeared. The response time for EEG changes to these steps in isoflurane concentrations was approximately 10 min, which is fast compared with the normal interval between manual notes in the anaesthesia log.

The shift to a red period (black in figure 3; areas C, D) after approximately 2 h of recording may indicate that the patient reached deeper anaesthesia when the surgical procedure was less painful. The effect of the decreases in isoflurane concentration at the second and third < is clearly reflected by the reappearance of the yellow dominance (white in figure 3) in the class histogram.

Towards the end of the recording, the histogram shifted to blue and green classes (black area E in figure 3), indicating transition from medium to light, very light and drowsy state, similar to the shift noted at start of surgery (event o in figure 3; black area A).

In the majority of patients the yellow, medium depth dominated, but the interpatient variability was considerable. It is important to notice that, although the basic depth of anaesthesia was variable, the shift in the class profile was always related to the vaporizer adjustments. For example, the reaction from one patient receiving 1 MAC could be green (light) changing to yellow (medium) when receiving 1.25 MAC; alternatively another patient's basic depth of anaesthesia could be magenta (deep) with 1 MAC and red (very deep) when changing to 1.25 MAC. This shows that the EEG is a more sensitive test than the clinical evaluation, during medium anaesthesia.

Comparing clinical evaluation with the EEG analysis, it was obvious that, in some instances, the anaesthetist adjusted the isoflurane concentration, without knowing the result of signal processing. In these cases the EEG analysis "agreed" in the treatment of the patient.

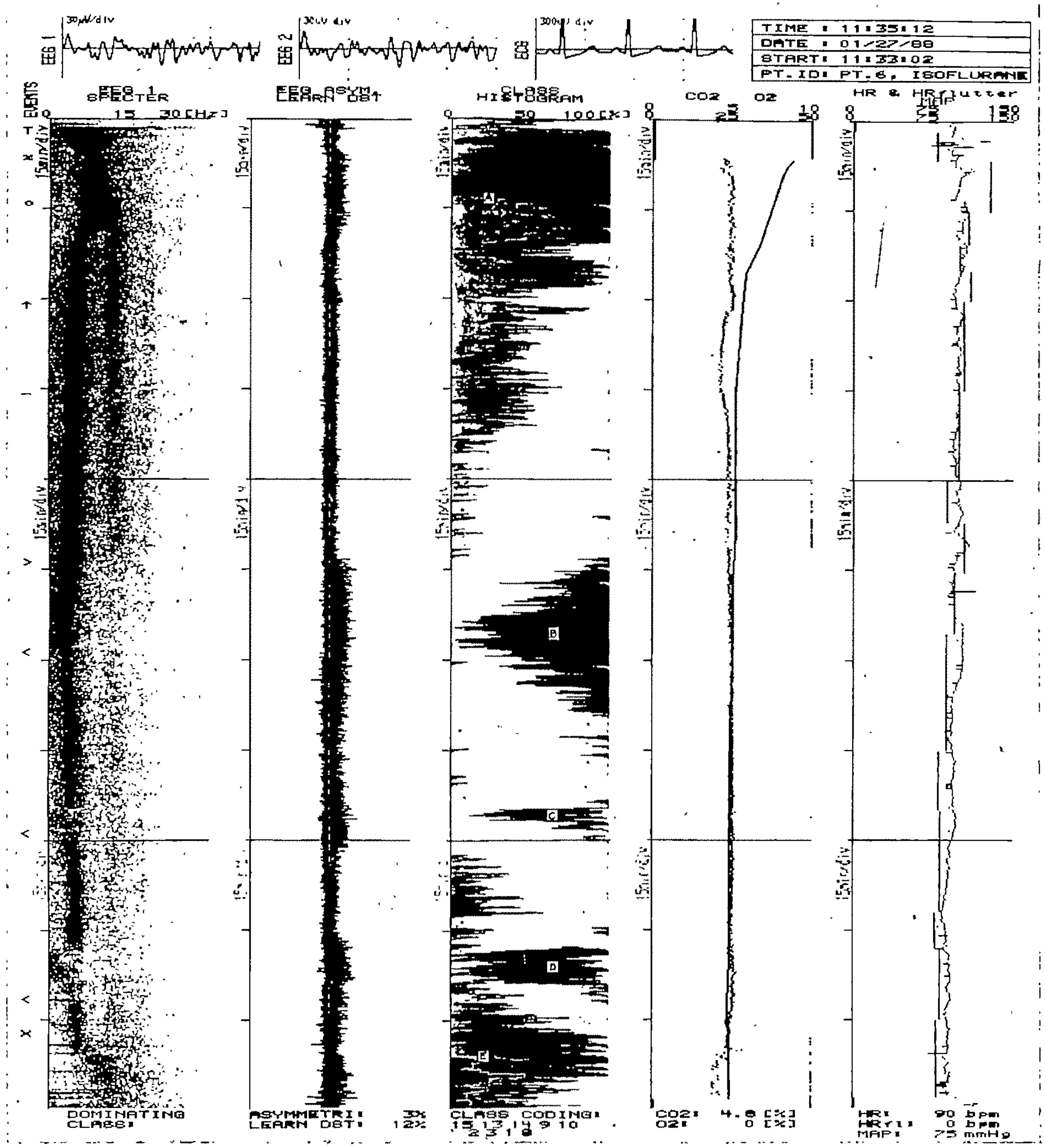
The computer program was not designed to detect burst suppression. A visual inspection of the EEG strip chart in periods with isoflurane concentrations exceeding 1.5 MAC showed no burst suppression.

In all patients slight hyperventilation was induced according to the procedure. This caused no change in the class profile in any of the patients. As expected in a non-critical surgical procedure, the asymmetry parameter was unchanged in all patients.

DISCUSSION

Intraoperative monitoring of the EEG activity has been used mainly during anaesthetic procedures in which cerebral perfusion and metabolism are at risk. Several types of monitoring system have shown to be of help as warning systems [18]. In contrast, the use of EEG monitoring as a guide to depth of anaesthesia is controversial and un-

FIG. 3. Black and white version of a hard copy record from a patient monitored during 2 h 45 min of isoflurane anaesthesia. Vertical axis is time. Data from the EEG are displayed in the three columns to the left, the traditional physiological parameters in the two columns to the right. Events during anaesthesia are marked along the time axis at the left: T = thiopentone; x, X = start and stop of anaesthesia; o = start of surgery; †, — = start and stop of hyperventilation; >, < = increase and decrease in isoflurane concentration. The left column shows a DSA plot for one of the EEG recordings (horizontal axis is frequency in Hz). The second column shows symmetry between the two hemispheres (red on colour record; left of added white line here) and spectral similarity between the actual EEG sequence and the most likely class in the learning set (green on colour record; right of added white line here). The column in the middle shows the class histogram of the classification of the EEG activity. On the original colour record, the classes are colour-coded according to the depth of anaesthesia as defined in figure 2; here, white areas correspond to yellow on the colour record, and labels A–E have been added to identify areas of dark blue, light blue plus green (A, E) and of magenta plus red (B–D). The fourth



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DOMINATING CLASS:
ASYMMETRI: 3%
LEARN DST: 12%
CLASS CODING: 15 13 14 9 10 2 3 1 8
CO2: 4.8 [%]
O2: 0 [%]
HR: 90 bpm
HRfl: 0 bpm
MAP: 75 mmHg

column shows end-tidal carbon dioxide concentration (CO2/black on colour record: 0–10 %) and inspiratory oxygen concentration (O2/red on colour record; more continuous line here: 0–50 %). The column to the right shows heart rate (HR/green on colour record, 0–150 beat min^{-1}; the width of this line represents the beat to beat variation in heart rate) and mean arterial pressure (MAP/blue on colour record; thicker, continuous vertical lines here: 0–150 mm Hg). The screen display during on-line analysis includes the last 1 h of the recording. The traces at the top are the raw signals of EEG and ECG displayed in 2-s segments for quality control during recording. The frame to the right is patient identification. The numbers below the columns are instantaneous displays of the variables.

reliable [13]. The reason for this could be that most investigations have focused on recordings in which critical physiological variables show a considerable degree of instability.

In the present work, our intention was to investigate the changes in brain activity related to the depth of anaesthesia in healthy subjects. Major efforts were made to keep basic physiological variables constant during monitoring.

Many investigators have reported disappointing results, with no correlation between EEG frequency, amplitude and depth of anaesthesia. In particular, the changes have been shown to be specific for the anaesthetic agent used [7]. Nevertheless, many attempts have been made to visualize the EEG signal in a compressed and simplified form, such as CSA-plot or DSA-plot [10, 11], in order to give the anaesthetist the opportunity to compare the clinical evaluation of anaesthetic depth with an on-line signal interpretation.

Using computerized signal processing, a great number of variables and features can be extracted, which represent information undetectable by simple visual inspection of the EEG signal. The present investigation of the EEG involves autoregressive modelling and clustering analysis in order to define a set of basic classes of activity, representing different depths of anaesthesia.

The set of basic classes was used as learning set for classification of EEG activity. The presentation of the result of classification in a class probability histogram demonstrated a high degree of simplicity. At the different depths of anaesthesia more than two classes were seldom represented.

The learning set was common and derived specifically from the isoflurane series. By this technique, the class histogram shows a significant profile of class occurrence related to the depth of anaesthesia. The difference seen in some patients between the profile of the class histogram and the clinical level of anaesthesia reflects the fact that the features displayed are more sensitive than the clinical evaluation. Even though some patients had a different class profile during the same clinical level of anaesthesia, a change to lighter or deeper clinical levels caused a stereotyped shift in class histogram to profiles representing the same trend.

In previous investigations it has been found that spectral edge frequency, centre frequency and mean energy content in the conventional frequency bands are valuable indicators of cerebral hypoxia. In the present work we found no information in these features related to depth of anaesthesia and we conclude that the sensitivity is too low inside the therapeutic range of isoflurane concentration. This indicates the necessity of implementing specific common sets of basic patterns corresponding to the actual combination of anaesthetics used. In our view, the generation of this reference material will be a major task in the construction of monitoring systems in the future.

ACKNOWLEDGEMENT

This study was supported by the Danish Technical Research Council and the Danish Medical Research Council.

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Br. J. Anaesth. (1989), **63**, 44–50

LOW-DOSE SUFENTANIL–ISOFLURANE ANAESTHESIA FOR CORONARY ARTERY SURGERY

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SUMMARY

Haemodynamic changes and catecholamine responses were measured during anaesthesia with sufentanil (total dose 7 $\mu g\ kg^{-1}$) supplemented with isoflurane in 14 patients undergoing coronary artery surgery. Isoflurane was used to control systolic arterial pressure, which was allowed to decrease to 100 mm Hg. Mean inspired isoflurane concentration was 0.22 (SD 0.19)% (induction), 0.34 (0.18)% (pre-bypass) and 0.22 (0.17)% (post-bypass). During cardiopulmonary bypass 0.22 (0.13)% isoflurane was administered to control mean perfusion pressure. During induction and the pre-bypass period, significant decreases in systolic and diastolic arterial pressure, systemic vascular resistance and left ventricular stroke work index (LVSWI) ($P < 0.01$) were noted. The decrease in LVSWI with unchanged filling pressures indicated myocardial depression. Serum catecholamine concentrations remained at the pre-induction value until cardiopulmonary bypass, when a significant increase was noted. Tracheal intubation, sternotomy and sternal spread were not associated with hypertension or tachycardia. Clinical signs that could reflect myocardial ischaemia were not observed per-operatively. After operation, cardiac enzymes were within the normal clinical range and ECG was unchanged.

Patients with good left ventricular function are often at risk of hypertension with high-dose fentanyl–oxygen anaesthesia [1] Recently, sufentanil has been introduced into cardiac anaesthesia [2,3]. Compared with fentanyl, it has a greater potency, a higher receptor affinity and a higher therapeutic index [4]. In dogs, the degree of control of stress reactions is greater with sufentanil than with fentanyl [5]. However, several reports have shown that sufentanil is no more effective than fentanyl in suppressing hypertension or tachycardia [1,2,6].

We have examined the catecholamine and haemodynamic effects of an anaesthetic technique in which sufentanil (total dose 7 $\mu g\ kg^{-1}$) was supplemented with isoflurane in order to reduce the extent of hypertension during coronary artery surgery.

PATIENTS AND METHODS

The study was approved by the Ethics Committee of the University Hospital, Antwerp.

We studied 14 patients (11 male), with good left ventricular function (ejection fraction > 55% and left ventricular end-diastolic pressure < 14 mm Hg) undergoing elective coronary bypass surgery. Mean age was 55 (SD 7) yr, average weight 72.9 (8.7) kg (table I). All patients had angiographically proven coronary artery disease (two- or three-vessel disease), no patient had significant left main coronary artery stenosis.

Premedication consisted of fentanyl 2 $\mu g\ kg^{-1}$ plus droperidol 0.01 $mg\ kg^{-1}$ and glycopyrrolate 0.03 $mg\ kg^{-1}$ given i.m. 1 h before surgery, in addition to the normal oral medication appropriate to each patient.

In the operating room, the electrocardiogram (lead I, II and V5) was displayed continuously. Two large gauge venous cannulae and a 20-gauge Teflon radial arterial cannula were placed. A flow-directed balloon-tipped thermodilution catheter (7 French gauge, triple lumen catheter) was

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Accepted for Publication: January 19, 1989.
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TABLE I. *Clinical data of patients. NYHA class = New York Heart Association classification; AMI = acute myocardial infarction; A = atenolol; Ac = acebutolol; I = isosorbide; M = metoprolol; N = nifedipine; T = tildiazem*

Patient No.	Age (yr)	Weight (kg)	NYHA class	AMI	Hyper-tension	Medication
1	57	58	II	–	–	M:N:I
2	53	77	III	+	–	M:T:I
3	52	82	III	+	–	A:T:I
4	57	82	IV	–	+	N:I
5	42	73	III	–	–	Ac:N:I
6	67	56	IV	–	+	M:N:I
7	61	74	III	–	–	A:I
8	50	82	III	–	–	A:I
9	60	68	III	+	–	N:I
10	49	80	II	–	–	N:I
11	61	65	III	+	–	A:I
12	56	69	III	–	–	M:N:I
13	56	80	III	+	–	Ac:N:I
14	46	74	III	–	–	M:N:I

introduced into the pulmonary artery via the right internal jugular vein using a 7 French gauge introducer. All these lines were placed under local anaesthesia. Arterial measurements were checked for adequate dynamic response [7].

After a 10-min period of stabilization, control measurements (= T1) of heart rate, systolic, diastolic and mean arterial pressure, systolic and diastolic pulmonary artery pressure, pulmonary capillary wedge pressure and central venous pressure were made. Cardiac output was measured (in triplicate) by thermodilution using 10 ml of 5 % dextrose in water at 0 °C injected during the expiratory phase. From these data cardiac index, systemic vascular resistance and left ventricular stroke work index were calculated using standard formulae.

Anaesthesia was induced with diazepam 0.1 mg kg^{-1}, pancuronium 0.1 mg kg^{-1} and sufentanil 4 µg kg^{-1} given in sequence over 30 s. After loss of consciousness, the patient's lungs were ventilated manually by mask with oxygen. Isoflurane was added to the inspired gas in a variable concentration according to the systolic arterial pressure, which was allowed to decrease to 100 mm Hg. After tracheal intubation, ventilation was controlled mechanically with a 900 C Siemens Servo Ventilator (60 % oxygen in air, rate 12 b.p.m. with a tidal volume according to the arterial $P\text{co}_2$, which was maintained at 4.7–5.3 kPa).

During the pre-bypass period the inspired isoflurane concentration was adjusted to maintain the systolic arterial pressure at approximately 100 mm Hg. Inspired isoflurane concentration was recorded from the setting of the isoflurane vaporizer which was calibrated using an infra-red flow-through photometer. Before skin incision and before sternotomy, an additional dose of sufentanil 1 µg kg^{-1} was given.

During the pre-bypass period haemodynamic data were recorded and calculated at the following time intervals: 3 min after induction (= T2), 3 min after intubation (= T3), before and 3 min after sternotomy (= T4 and T5) and before aortic cannulation (= T6). At these time intervals, and at point T1, 10-ml blood samples were collected from the radial artery catheter into lithium–heparin tubes. Plasma concentrations of adrenaline and noradrenaline were measured using high pressure liquid chromatography (HPLC) with electrochemical detection [8] (detection limit 20 pg ml^{-1}).

During the pre-bypass period, the following variables were evaluated for the presence of myocardial ischaemia at 5-min intervals: ST-depression (> 0.1 mV in V5 or > 0.2 mV in the peripheral leads), increased pulmonary capillary wedge pressure (PCWP) or the appearance of prominent PCWP v-waves.

Before starting cardiopulmonary bypass (CPB), heparin 300 units kg^{-1} and a subsequent dose of pancuronium 0.1 mg kg^{-1} were given. The pump prime consisted of 2000 ml of an isotonic solution and 500 ml of a 20 % human albumin solution. CPB was conducted using a Bentley TM-10 disposable bubble oxygenator and Stöckert/Cobe roller pumps. During CPB the lungs were not ventilated, but allowed to collapse partially with a static inflation pressure (using air) of 3 mm Hg. Patients were cooled during CPB to a rectal temperature of 25 °C. Non-pulsatile flow was used at 2.4 litre $min^{-1} m^2$ with a perfusion pressure of 70–80 mm Hg, using phenylephrine or isoflurane when necessary. Isoflurane was delivered from a calibrated isoflurane vaporizer.

Myocardial protection was provided according to the surgeon's preference. St Thomas Hospital cardioplegia solution or Bretschneider cardioplegia solution was used, with topical cooling of the myocardium. In those patients in whom intermittent aortic cross clamping was used, lidoflazine 1 mg kg^{-1} was given i.v. before starting CPB. Forty-five minutes after starting CPB, a blood sample was obtained for catecholamine assay.

After CPB, when haemodynamic variables were stable and protamine has been given, sufentanil 1 μg kg^{-1} was given and isoflurane was added to the inspired gas when necessary. At this point haemodynamic data were recorded and calculated (= T7).

After operation, haemodynamic variables were obtained and calculated at the following times after arrival in the intensive care unit: 30 min (= P1), 2 h (= P2), 6 h (= P3) and 12 h (= P4). During this 12-h period, the need for vasodilators or inotropic drugs was recorded. The trachea was extubated when the following conditions pertained: the patient was fully awake; there was no surgical bleeding; haemodynamic indices were stable; rectal temperature was $\geqslant$ 36.5 °C; a trial of spontaneous ventilation was not associated with an increase in heart rate, arterial pressure, hypoxaemia or hypercapnia. The period from termination of surgery to tracheal extubation was recorded.

Results were analysed for statistical significance using analysis of variance for repeated measurements. Where appropriate, analysis of variance was followed by the Scheffe F test. Significant difference was accepted at $P < 0.05$.

RESULTS

Induction and intubation

During induction, two patients had an increase in systolic arterial pressure of more than 15 % above pre-induction value, together with an increase in heart rate of more than 20 % during i.v. induction. One of these patients was receiving β-adrenoreceptor antagonist therapy. In three other patients an increase in heart rate of more than 15 % of control value was noted without an increase in arterial pressure. All these patients were taking β-adrenoreceptor antagonists. These observed increases in heart rate and systolic arterial pressure were transient, lasting not more than 2 min. Adding isoflurane to the inspired gas (table II) was sufficient to control these changes. A transient truncular rigidity after the bolus injection of sufentanil 4 μg kg^{-1} was observed in two patients, but manual ventilation of these patients by mask was possible. Haemodynamic variables (table III) remained stable during intubation; when haemodynamic data before (= T2) and 3 min after intubation (= T3) were compared, no significant differences were found for the observed and calculated haemodynamic variables. Between T2 and T3, heart rate and systolic arterial pressure were unaffected also by laryngoscopy. Clinical signs that could reflect myocardial ischaemia were not observed during induction and intubation.

Pre-bypass period

There were no differences in haemodynamic variables before (= T4) and 3 min after sternotomy (= T5) (table III), although the hypotension observed after induction remained significant ($P < 0.01$). Systolic pulmonary artery

TABLE II. *Anaesthetic requirements*

	Sufentanil (μg kg^{-1})	Isoflurane inspired concn (%)	
		Mean (SD)	Range
Induction + intubation	4	0.22 (0.19)	0.00–0.78
Pre-bypass period	2	0.34 (0.18)	0.16–0.88
Bypass period	—	0.22 (0.13)	0.06–0.53
Post-bypass period	1	0.22 (0.17)	0.00–0.60

TABLE III. *Peroperative haemodynamic data (mean (SD)). T1 = before induction; T2 = 3 min after induction; T3 = 3 min after intubation; T4 = before sternotomy; T5 = 3 min after sternotomy; T6 = before aortic cannulation; T7 = after cardiopulmonary bypass. HR = heart rate; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure; CI = cardiac index; SVR = systemic vascular resistance; PCWP = pulmonary capillary wedge pressure; CVP = central venous pressure; LVSWI = left ventricular stroke work index; SPP = systolic pulmonary artery pressure; DPP = diastolic pulmonary artery pressure. Significant difference compared with corresponding T1 value:* *P < *0.05*; **P < *0.01*

	T1	T2	T3	T4	T5	T6	T7
HR (beat min^{-1})	65 (14)	70 (11)	71 (12)	67 (10)	66 (11)	67 (12)	80 (12)**
SAP (mm Hg)	143 (20)	108 (14)**	103 (12)**	105 (10)**	103 (10)**	102 (11)**	107 (21)**
DAP (mm Hg)	67 (13)	52 (8)**	51 (8)**	55 (9)**	52 (5)**	52 (8)**	57 (9)*
MAP (mm Hg)	93 (15)	70 (10)**	68 (11)**	72 (9)**	69 (8)**	70 (10)**	74 (14)**
CI (litre min^{-1} m^{2})	3.2 (0.5)	3.2 (0.5)	3.3 (0.5)	3.0 (0.4)	3.0 (0.5)	3.0 (0.6)	2.8 (0.5)
SVR (dyn s cm^{-5})	1129 (239)	834 (177)**	792 (216)**	916 (223)	906 (145)	918 (212)	966 (312)
PCWP (mm Hg)	13 (4)	13 (3)	12 (3)	13 (3)	12 (3)	11 (3)	17 (4)**
CVP (mm Hg)	9 (3)	9 (4)	9 (4)	9 (3)	7 (3)	7 (3)	13 (5)**
LVSWI (g m m^{-2})	65 (16)	45 (7)**	43 (5)**	44 (6)**	44 (8)**	42 (7)**	36 (9)**
SPP (mm Hg)	30 (7)	27 (5)	28 (6)	27 (5)	25 (4)	23 (5)	33 (7)
DPP (mm Hg)	12 (5)	13 (5)	12 (5)	12 (5)	11 (4)	10 (4)	16 (5)

TABLE IV. *Surgical data.* † *Mean intermittent cross-clamping time*

			No. of distal anastomoses	
Patient No.	Myocardial protection	Aortic cross clamping time	With saphenous vein	With mammary artery
1	St Thomas	41 min	3	1
2	St Thomas	85 min	3	2
3	St Thomas	70 min	6	—
4	Lidoflazine	9 min 24 s†	3	1
5	Lidoflazine	9 min 30 s†	5	1
6	Lidoflazine	11 min 45 s†	4	1
7	Lidoflazine	9 min†	3	2
8	Bretschneider	84 min	5	—
9	Lidoflazine	8 min 31 s†	3	1
10	Bretschneider	98 min	4	1
11	Lidoflazine	8 min 42 s†	4	1
12	Bretschneider	75 min	4	1
13	Lidoflazine	8 min 21 s†	4	—
14	Lidoflazine	9 min 30 s†	3	1
Mean		76 (SD 19) min		

pressures remained at the pre-induction value until the time of aortic cannulation, when there was a significant ($P < 0.05$) decrease. Vasodilator therapy was not necessary to control arterial pressure during the pre-bypass period. Fluid requirement during the pre-bypass period was provided by 5% dextrose in Ringer's lactate 0.34 (0.10) ml kg^{-1} min^{-1}.

Bypass period

Mean duration of cardiopulmonary bypass was 136 (21) min. All patients received isoflurane during CPB to control mean perfusion pressure (mean 0.22 (0.13)%; range 0.06–0.53%) (table II). Two patients were given phenylephrine (0.2 mg and 0.3 mg, respectively) during the first minutes of CPB. In six patients a cardioplegic solution was used. Mean aortic cross clamping time for these patients was 76 (19) min (table IV). In the other eight patients, distal anastomosis with the coronary arteries were performed during intermittent aortic cross clamping. Mean aortic cross clamping time was 9.2 (1.6) min for each distal anastomosis.

TABLE V. *Changes in mean (SD) serum catecholamine concentration during pre-bypass period and cardiopulmonary bypass. T1 = before induction; T2 = 3 min after induction; T3 = 3 min after intubation; T4 = before sternotomy; T5 = 3 min after sternotomy; T6 = aortic cannulation; CPB = 45 min after initiating cardiopulmonary bypass. Significant difference compared with T1:* *P < *0.05;* **P < *0.01*

	T1	T2	T3	T4	T5	T6	CPB
Noradrenaline (pg ml^{-1})	361 (154)	357 (143)	383 (142)	262 (101)	294 (104)	405 (182)	721 (314)**
Adrenaline (pg ml^{-1})	262 (132)	85 (22)	67 (21)	58 (26)	58 (30)	65 (15)	547 (286)*

TABLE VI. *Postoperative haemodynamic data (mean (SD)).* n = *13; one of the patients investigated was excluded from the postoperative observation period because of postoperative bleeding requiring surgical intervention. T7 = after cardiopulmonary bypass; P1 = 30 min after arrival in the intensive care unit; P2 = 2 h after arrival, P3 = 6 h after arrival, P4 = 12 h after arrival. Significant difference compared with corresponding P1 value:* *P < *0.05;* **P < 0.01

	T7	P1	P2	P3	P4
HR (beat min^{-1})	80 (10)	86 (12)	99 (15)**	96 (11)**	89 (10)
SAP (mm Hg)	105 (20)	119 (17)	130 (11)*	135 (30)**	121 (15)
DAP (mm Hg)	58 (9)	60 (11)	65 (9)	64 (9)	59 (8)
MAP (mm Hg)	76 (13)	80 (13)	87 (9)	87 (16)	78 (8)
CI (litre min^{-1} m^{2})	2.8 (0.4)	3.0 (0.9)	3.3 (0.9)	3.3 (0.8)	2.9 (0.6)
SVR (dyn s cm^{-5})	1003 (292)	1113 (388)	1084 (339)	1055 (328)	1064 (362)
PCWP (mm Hg)	17 (5)	8 (3)**	10 (2)**	12 (3)**	10 (3)**
CVP (mm Hg)	12 (5)	9 (5)	10 (4)	11 (3)	10 (3)
LVSWI (g m m^{-2})	36 (10)	38 (12)	39 (10)	40 (11)	34 (8)
SPP (mm Hg)	34 (7)	26 (7)	31 (8)	31 (7)	32 (7)
DPP (mm Hg)	16 (5)	11 (5)	11 (5)	14 (3)	12 (4)

Post-bypass period

All patients were weaned easily from cardiopulmonary bypass without inotropic support. When haemodynamic variables after cardiopulmonary bypass were compared with corresponding pre-induction values, a significant difference was present for the following variables: heart rate (increased), systolic, diastolic and mean arterial pressure (decreased), pulmonary capillary wedge pressure and central venous pressure (increased) and left ventricular stroke work index (decreased) (table II). When these post-bypass data were compared with the haemodynamic data before aortic cannulation, a significant difference ($P < 0.01$) was found only for heart rate, pulmonary capillary wedge pressure and central venous pressure.

Catecholamine responses

Serum concentrations of catecholamines were unchanged during the pre-bypass period, but increased significantly 45 min after cardiopulmonary bypass was initiated (table V).

Postoperative period

One patient was excluded from the postoperative observation period because of serious postoperative bleeding. Compared with the haemodynamic variables after CPB, there was a significant decrease in pulmonary capillary wedge pressure at the four postoperative observations (table VI). Heart rate and systolic arterial pressure increased significantly.

During this 12-h observation period, 10 of 13 patients were treated with vasodilator drugs to control postoperative hypertension or to decrease a high systemic vascular resistance (nine patients received nitroprusside to a maximum dose of 4 μg kg^{-1} min^{-1} and one received nitroglycerine to a maximum dose of 3 μg kg^{-1} min^{-1}). One other patient required inotropic support (dopamine 6 μg kg^{-1} min^{-1}) during the first 7 h in the intensive care unit, because of a low output state. The trachea was extubated at 567 (48) min (range 360–690 min) after the end of the surgical procedure. Cardiac enzymes (CK, CK-MB, ALAT, ASAT) were within the normal clinical range in all patients. Postoperative ECG showed no additional changes compared with preoperative ECG in all patients.

DISCUSSION

Although high-dose opioid–oxygen anaesthesia has become a popular technique for patients undergoing coronary artery surgery, we have chosen a balanced anaesthetic technique in these patients (with good left ventricular function) in order to reduce the frequency of hyperdynamic reactions during stressful stimuli, produce controllable myocardial depression and shorten the period of postoperative respiratory depression.

In this study intubation, sternotomy and sternal spread had no effect on heart rate or systolic arterial pressure. At no point during anaesthesia and surgery was vasodilator therapy necessary to control arterial pressure. This haemodynamic stability was not present when sufentanil [2,3,6,9] or isoflurane [10] was used as the sole anaesthetic agent. The reason for this is probably related to adequate β-adrenoreceptor blockade in most of our patients, calcium channel blocking therapy and myocardial depression resulting from this balanced anaesthetic technique.

Thirty-five percent of patients receiving β-adrenoreceptor therapy exhibited a tachycardia of more than 15% after induction. This is larger than we commonly observe with fentanyl–isoflurane anaesthesia. A possible reason for this is the combined use of pancuronium bromide and sufentanil [11]. Isoflurane may cause reflex tachycardia [12], but in this study heart rate decreased when isoflurane was added to the inspired gas.

Myocardial depression, induced by inhalation anaesthetics, is thought to be desirable in patients with coronary artery stenosis, especially those with well preserved ventricular function [13,14]. We prefer isoflurane, as cardiac output may be better maintained than with halothane [15,16]. Isoflurane has been demonstrated to be superior to halothane in controlling peroperative hypertension [17]. Furthermore, during cardiopulmonary bypass isoflurane may be used to control mean perfusion pressure because of its vasodilating properties [12].

Isoflurane has been thought to induce coronary steal in patients with coronary artery disease, resulting in decreased myocardial lactate extraction or even lactate production [10,18] and it has been questioned if isoflurane may be given safely to patients with coronary artery stenosis [19]. However, some important distinctions can be made between the study of Reiz and colleagues [18] and that of Moffitt and colleagues [10]. The patients studied by Reiz were older and had more severe left ventricular function impairment. Isoflurane was given in a fixed concentration of 1.0% and heart rate increased significantly. Furthermore, myocardial lactate extraction decreased only in patients who also had clinical evidence of myocardial ischaemia (ST-segment depression or T-wave inversion). In the study of Moffitt, five of 10 patients had pre-existing ST-segment depression before induction; in two of these ST-segment depression increased with induction. Myocardial lactate production has also been demonstrated during high-dose fentanyl anaesthesia [20], and was also associated with hyperdynamic disturbances.

O'Young reported that when isoflurane was given to control hypertension following sternotomy, no myocardial lactate production was observed and clinical signs of myocardial ischaemia, when present, disappeared [21]. This suggests that preventing breakthrough hypertension and tachycardia during or following tracheal intubation and sternotomy is the most important factor in protecting the myocardium from ischaemia and not the use of any particular anaesthetic agent. With the moderate concentrations of isoflurane used in this study, there was no evidence of myocardial ischaemia induced by this agent.

Suppression of the stress response during the pre-bypass period with sufentanil–oxygen anaesthesia has been demonstrated by many authors [6,9,22]. Flezzani and colleagues reported that isoflurane produced a dose-related decrease in plasma cortisol concentrations during cardiopulmonary bypass [23]. However, we could not demonstrate a suppression of catecholamine responses during bypass when isoflurane was given to control mean perfusion pressure.

One of the reasons for our choice of a balanced anaesthetic technique with low-dose sufentanil was to shorten the period of postoperative opioid-induced respiratory depression. However, compared with most studies in which sufentanil was used as sole anaesthetic agent (in a mean dose ranging from 12.9 to 19.9 $\mu g\ kg^{-1}$) [3,24], extubation time could not be reduced. This suggests that opioids *per se* in these doses are not the most important determinant for tracheal extubation.

This was demonstrated also by a study by Moffitt and colleagues [10], in which isoflurane was used as the sole anaesthetic agent and extubation time was comparable. Cardiovascular stability and the absence of hypoxaemia during spontaneous ventilation seem to be the important determinants for tracheal extubation.

The frequency of use of vasodilator therapy after operation (77 %) is rather high in this study. This is influenced by the policy of the intensive therapy unit, where treatment is started when systolic pressure is more than 130 mm Hg or systemic vascular resistance is more than 1500 dyne s cm^{-5}. Only two of 14 patients had an acute hypertensive reaction after operation, compared with a 61 % incidence of acute hypertension during the first 5 h after operation reported elsewhere [25]. This is related to the almost routine use of vasodilator therapy and the β-receptor antagonist therapy given before surgery.

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Br. J. Anaesth. (1989), **63**, 51–55

EFFECTS OF THIOPENTONE ON MEDIAN NERVE SOMATOSENSORY EVOKED POTENTIALS†

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Intraoperative monitoring of somatosensory evoked potentials (SSEP) is used increasingly during central nervous system surgery to improve intraoperative monitoring of neural tracts at risk. Monitoring of these potentials is made difficult by technical, physiological, surgical and anaesthetic changes which may cause alterations in neural function. Anaesthetic agents can produce dramatic alterations in SSEP which may mimic neural injury. This is of particular concern at the beginning of the anaesthetic, when marked physiological changes and positioning may place neural structures at risk before surgery.

Several studies have demonstrated alterations in SSEP with various anaesthetic agents. Many of these changes are dose-related [1] in a manner similar to dose-related effects on the electroencephalogram (EEG). Few studies have examined carefully the time-related effects of these agents. If an effect on SSEP is based on an anaesthetic effect, the alteration should be consistent with the time course and known method of action of the agent. Studies of the effect of thiopentone on the EEG show a time course similar to anaesthetic effect [2].

Thiopentone is a commonly used induction agent that has been shown to alter SSEP, but a careful time-related study of induction doses has not been conducted. This study was designed to examine the time course of SSEP effects of an induction bolus of thiopentone on the median nerve SSEP.

SUMMARY

We have studied the effects of an i.v. bolus of thiopentone 4 mg kg^{-1} on the median nerve somatosensory evoked potentials (SSEP) in 15 unpremedicated patients. The latency and amplitude of the SSEP response over the second cervical vertebra (SC) and sensory cortex (P_{15}, N_{20}, P_{25}) were recorded before and for 12 min after injection. Data were analysed at 0, 4, 8 and 12 min for time-related alterations. Cortical amplitude was variable, with a tendency to decrease ($P < 0.03$). There was a statistically significant but clinically insignificant transient increase in latency of the cortical N_{20} ($P < 0.008$), and interwave conduction times of SC to P_{15} ($P < 0.007$) and SC to P_{25} ($P < 0.039$). The relation of these results to the proposed mechanism of thiopentone action at synapses is discussed.

PATIENTS AND METHODS

Fifteen ASA Class I and II patients scheduled to undergo thoracic or lumbar spinal surgery with SSEP monitoring gave written informed consent to participate in this study, which was approved by the Institutional Review Boards. Patients with possible neurological abnormalities in the median nerve pathway or intracranial pathology were excluded.

Unpremedicated patients came to the operating room where a catheter was inserted into a vein and the overnight fluid deficit was replaced over 30 min using 2.0 ml kg^{-1} h^{-1} of 5% dextrose in lactated Ringer's solution. Routine anaesthesia monitoring included precordial stethoscope, spirometer, continuous electrocardiogram, automated arterial pressure, temperature and end-tidal carbon dioxide measurement.

Disc recording electrodes with electrode paste

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†Presented in part at the Annual Meeting of the International Anesthesia Research Society in Las Vegas, Nevada, March 1986.

were attached with collodion after skin abrasion. The active electrode for cortical recording was placed over the primary somatosensory cortex for the arm being stimulated, 2 cm posterior to C_3 (right hand) or C_4 (left hand), with the reference electrode at F_z (International 10–20 system). The active electrode for cervical recording was placed at the inion (SC) with F_z as the reference electrode. A silver–silver chloride ground electrode was placed on the shoulder. All electrode impedances were less than 3000 Ω, and channel electrodes were matched within 1000 Ω. Median nerve SSEP were obtained using stimulation at the wrist with a bipolar bar electrode following application of electrode gel and gentle skin abrasion. Constant current stimulation using 300-μs square wave impulses was used at 5.7–8.7 Hz at a current 1 mA greater than that sufficient to produce a motor response.

For each averaged waveform, 250 artefact free responses were obtained using a Nicolet Pathfinder II or Nicolet CA-1000/DC-2000 signal averager (Nicolet Biomedical, Madison, Wisconsin), using bandpass filtration of 5–250 Hz (60 Hz notch filtration was not used) and an analysis window of 50 ms. All acquired data were stored on magnetic discs for later analysis.

After satisfactory duplicate baseline recordings were obtained, thiopentone 4 mg kg^{-1} was given i.v. over 30 s. The SSEP, arterial pressure (AP) and heart rate (HR) were recorded every 1 min after the dose, and ventilation of the lungs was assisted manually as necessary with a facemask using 40% oxygen in air to maintain end-tidal carbon dioxide partial pressure at 4.7–6.0 kPa. All patients had a body temperature exceeding 36.5 °C at the conclusion of the study. SSEP data were acquired at 1-min intervals for 9 min, and then every 3 min until 30 min after injection. The patients then received an opioid-based anaesthetic (sufentanil or fentanyl) supplemented with 0.4% isoflurane or an infusion of thiopentone 1.5 mg kg^{-1} h^{-1} before tracheal intubation and surgery. Posterior tibial nerve SSEP were monitored during surgery.

Data from the waveforms were acquired after the study by recall of stored averages. Post-stimulus latency of the major cervical negative wave (SC) (approximately 15 ms) and the latencies of the primary cortical response waves (P_{15}, N_{20} and P_{25}) were recorded. The conduction times (CT) were calculated as intervals between various peaks. Cortical amplitude was taken as the voltage from the N_{20} trough to the P_{25} peak of the cortical response.

SSEP latencies, conduction times, amplitudes and physiological variables (arterial pressure and heart rate) at 0, 4, 8 and 12 min were compared using Friedman two-way analysis of variance; differences were confirmed with the Wilcoxon matched pairs signed ranks test. Statistical significance was considered when $P < 0.05$.

RESULTS

We studied seven women and eight men, mean age 42 yr (range 18–81 yr), average height 172 cm (range 157–185 cm) and weight 72 kg (range 49–90 kg). No patient had a haemoglobin concentration less than 11.7 g dl^{-1} or serum albumin concentration less than 3.5 g dl^{-1}. All patients tolerated the study well. Most patients were awake by 15 min from induction. By 18 min, 12 patients had recording of the SSEP stopped because they were awake or moving extremities such that further recordings could not be taken.

Only one patient did not awaken during the 30 min. Inadequate tracings beyond 12 min precluded study at later times. Figure 1 shows selected tracings of the cervical and cortical response of one patient in whom recordings were acceptable for 12 min. No patient expressed unpleasant recall of the study period.

There was no difficulty obtaining the post-stimulus latencies immediately after the bolus of thiopentone. A statistically significant change in latency ($P < 0.008$) occurred in the cortical N_{20} response (table I). Examination of figure 1 and assessment by Wilcoxon analysis demonstrated a significant difference between time 0 and later times, confirming the impression that the increase occurred quickly after injection (1–2 min) and resolved during the study period. However, the absolute latency increase was small. Changes in the latencies of the other cortical peaks were also small and not statistically significant.

Analysis of the interwave latencies between peaks (conduction times) revealed significant differences between the cervical response and cortical P_{15} ($P < 0.01$) and between the cervical response and cortical P_{25} ($P < 0.05$). Again, the major change occurred shortly after injection. As with the absolute latencies, the conduction time changes were small.

Baseline amplitudes ranged from 0.7 to 6.3 μV. The individual response of amplitude to thio-

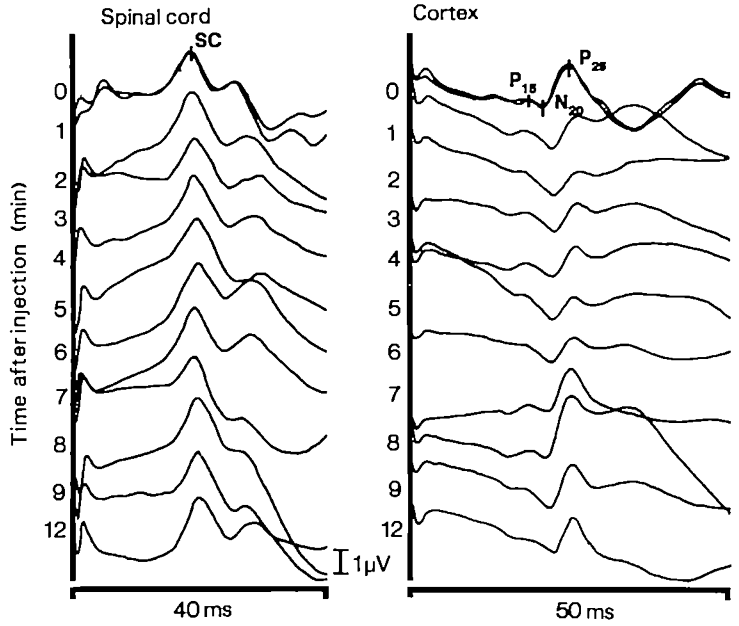

FIG. 1. SSEP responses recorded from the cervical and cortical electrodes as detailed in the text, before (0) and at 10 times following the injection of thiopentone in one patient. Cervical spinal cord response (SC): negative response at the active electrode is upward. The peaks evaluated in the cortical response (P_{15}, N_{20}, P_{25}) are indicated: positive response at the active electrode is shown upward.

TABLE I. *Effects of thiopentone on SSEP latency and amplitude and cardiovascular variables (mean (SD)). One patient was excluded from analysis at 12 min only.* *$P < 0.05$

	Baseline	4 min	8 min	12 min
Latency (ms)				
SC	15.54 (1.59)	15.34 (1.51)	15.48 (1.61)	15.48 (1.49)
P_{15}	17.35 (1.43)	17.91 (1.83)	18.06 (1.59)	17.91 (1.94)
N_{20}*	20.79 (1.79)	21.68 (2.22)	21.69 (2.08)	21.61 (2.62)
P_{25}	25.47 (2.57)	25.85 (3.38)	25.53 (2.94)	25.89 (3.00)
Amplitude (µV)				
N_1–P_2*	3.51 (1.93)	2.67 (1.79)	2.78 (1.75)	2.46 (1.41)
Physiological variables				
SAP (mm Hg)	133 (16)	120 (16)	121 (17)	120 (17)
DAP (mm Hg)	85 (12)	77 (14)	75 (11)	75 (13)
HR (beat min^{-1})	77 (11)	79 (13)	74 (4)	73 (11)

pentone was variable; however, the mean amplitude of all patients tended to decrease significantly and outlasted the period of hypnosis produced by the drug ($P = 0.03$) (table I). There did not appear to be any relationship between amplitude or latency and awakening time.

There were significant changes in systolic and diastolic arterial pressure ($P < 0.0008$ and $P < 0.012$, respectively), but not in heart rate or pulse pressure (table I).

DISCUSSION

This study has demonstrated that thiopentone altered the short latency median nerve SSEP responses during at least the first 12 min after induction of anaesthesia in unpremedicated patients. The most marked change was a reduction in cortical amplitude; however, the early response was variable. Although significant for some values, the absolute degree of change of latency values was small.

Variability of cortical amplitude has been reported in other studies in animals and man. An eventual decrease in amplitude after thiopentone has been observed consistently [3, 10]. In these studies, the final stabilization of this amplitude effect was observed by 6–9 min [5], 12–15 min [6] or 30 min [6]. This is consistent with our study, in which stabilization of the amplitude occurred usually by 3–10 min.

The latency changes seen are also consistent with previous studies which demonstrated marked alteration in late cortical peaks with minimally altered early responses [3, 7–11]. The increase in latency of cortical peaks was exaggerated with later peaks (table I). This progressive effect at later latency has been observed by Angel, Berridge and Unwin [6], Clark and Rosner [12] and Shaw and Cant [13] and has been suggested as consistent with an effect of barbiturates on synaptic transmission [4]. The assessment of late cortical peaks in this study is limited because of the high rate of stimulation.

Alterations in physiological variables associated with i.v. injection of thiopentone observed in this study are similar to those reported by others [14–18]. It is unlikely that the change in heart rate or decrease in arterial pressure are responsible for the amplitude and latency alterations, as the absolute magnitude of AP and HR changes was small. As body temperature and end-tidal carbon dioxide partial pressure were maintained constant, the changes observed were probably related to neural effects of the barbiturate.

It is notable that stabilization of the evoked potential changes occurred at a time similar to the stabilization of cardiovascular changes. This may suggest that the haemodynamic and cerebral events were consequences of drug delivery and dependent on drug concentrations at the effector sites. The early onset of these SSEP changes, as with the physiological variables, is consistent with the predicted delivery of thiopentone to the central nervous system within 1 min after i.v. injection [19].

A lack of correlation between time of awakening and the measured parameters of the evoked potentials was observed also in a study of drug-free schizophrenics given thiopentone [6]. It is of interest that the changes in latency and amplitude persisted beyond awakening. The effect is consistent with the known phenomena of acute tolerance [20]. Alternatively, the drug–effector interaction at the pathways of wakefulness may operate via a different mechanism.

Although the data reported here are generally consistent with previous reports, there are small differences between this study and other studies cited. In general, these differences concern latency changes in the lateral cortical peaks. Whereas some differences may relate to specific species, doses or barbiturate used, differences could result from the measurements used: the stimulating and recording variables used in this study are those used routinely by the authors, but differ from several of the studies cited. The high rate of stimulation limits assessment of late cortical peaks. Further, the choice of active recording sites may influence the recording of waves which could be recorded optimally at different locations (particularly late cortical waves).

All these patients had easily monitored evoked responses during the study period and for the remainder of the surgical period. This confirms the clinical impression that evoked response monitoring can be conducted following induction with thiopentone. However, as the amplitude of the cortical response is reduced, neural insults related to positioning or induction would be detected best by excessive latency change or alterations after the initial period of instability.

ACKNOWLEDGEMENT

The authors thank Arnold Carlvin, N.D.T., Janice Hamilton, N.D.T., and Ronald Hayden for technical assistance.

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Br. J. Anaesth. (1989), **63**, 56–59

TRANSDERMAL FENTANYL FOR THE RELIEF OF PAIN AFTER UPPER ABDOMINAL SURGERY

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SUMMARY

Transdermal fentanyl (n = 22) was compared with placebo (n = 18) in a double-blind study of pain after upper abdominal surgery. All patients also received i.v. morphine on demand for supplementary analgesia. The transdermal systems were applied 2 h before induction of anaesthesia and remained in situ *for 24 h. After operation, pain scores were significantly lower and peak expiratory flow rates significantly higher in the transdermal fentanyl group, who demanded significantly less morphine than the control group. Mean plasma fentanyl concentrations at 12 and 24 h were within the therapeutic range (1.5 and 2.0 ng ml^{-1}, respectively).*

Transdermal drug delivery systems are simple to use and permit reliable administration of drugs [1–6]. Fentanyl has been formulated into a transdermal therapeutic system (TTS-fentanyl, ALZA Corporation). In a previous study, we observed that plasma fentanyl concentrations during TTS-fentanyl therapy in patients undergoing upper abdominal surgery did not differ significantly from those in a matched group of patients receiving the same dose of fentanyl by i.v. infusion [7]. In the present study, we have investigated the efficacy of transdermal fentanyl as an analgesic regimen in patients undergoing upper abdominal surgery.

PATIENTS AND METHODS

After Ethics Committee approval and informed written patient consent, we studied 40 patients (ages 18–70 yr, weight 50–100 kg) undergoing elective upper abdominal surgery. None had clinical evidence of hepatic, respiratory, renal or psychiatric disease.

TTS-fentanyl is a rate-controlled drug delivery system which, in this study, was designed to deliver fentanyl 100 μg h^{-1} [7]. Patients were allocated randomly to receive TTS-fentanyl or TTS-placebo in this double-blind study. TTS-placebo was identical in design to TTS-fentanyl, except that the reservoir contained only normal saline. Two hours before surgery, the transdermal delivery system was placed on a hair-free area of the upper chest.

The anaesthetic regimen was the same in both groups. Anaesthesia was induced with thiopentone 5 mg kg^{-1} and maintained with 0.5–2% enflurane and 67% nitrous oxide in oxygen. Fentanyl 200 μg was given at induction of anaesthesia. Neuromuscular block was achieved by vecuronium 0.1 mg kg^{-1} at induction of anaesthesia and supplementary doses as required. The lungs were ventilated mechanically to maintain normocapnia. Neuromuscular block was antagonized with neostigmine 2.5 mg given with atropine 1.2 mg at the end of surgery.

Postoperative analgesia was standardized and administered by the Pharmacia Prominject programmable on-demand infusion pump [8]. The syringe contained a solution of morphine 4 mg ml^{-1} in normal saline. Immediately after surgery, the Prominject was programmed to deliver an on-demand bolus dose of 2.5 mg with a lock-out time of 10 min. Ninety minutes later, the pump was

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reprogrammed to deliver a bolus of 1 mg with a lock-out time of 20 min. This regimen was discontinued 48 h after the application of the transdermal system.

Pain was assessed at 4, 8, 12 and 24 h after the application of the patch. Patients were asked to grade their pain by pointing at a large scale marked 0–9 (0 = no pain; 9 = worst pain imaginable). At these times, peak expiratory flow rates (PEFR) were measured using a Micromedics Pocket Spirometer [9]. All observations were made by one of two investigators.

Arterial blood samples for analysis of gas tensions were taken by radial artery puncture under local anaesthesia while the patient breathed air, at 0, 12 and 24 h. Venous blood also was taken at these times. Plasma was separated immediately and stored at −20 °C. Plasma fentanyl concentrations were measured subsequently by radioimmunoassay [10].

Patients were withdrawn from the trial if the ventilatory rate decreased to less than 8 b.p.m. for more than 5 min. Nausea and vomiting were treated by prochlorperazine 12.5 mg i.m.

Data were analysed by Chi-square, Mann–Whitney or Student's *t* test as appropriate.

RESULTS

There were no significant differences between the groups with respect to age, sex, weight, duration and type of surgery (table I). The TTS-fentanyl group demanded significantly less morphine 90 min after surgery ($P < 0.01$) and in the first 24 h ($P < 0.01$) (table II). Two patients in the placebo group demanded the maximum available amount of morphine 90 min after surgery (pain scores 7 and 9), but no patient demanded the maximum thereafter. Mean requirement for morphine was less also in the second 24 h, after the patch had been removed ($P < 0.05$). Median pain scores and ranges during the first 24 h (table III) were significantly less in the TTS-fentanyl group at each time interval. Mean PEFR at 12 h and at 24 h expressed as a percentage of the preoperative value (table IV) was significantly greater in the TTS-fentanyl group ($P < 0.01$ and $P < 0.05$, respectively).

TABLE I. *Patient data (mean (SD)). No significant differences*

Group	Age (yr)	Sex (M/F)	Weight (kg)	Duration of surgery (min)	Type of surgery
Fentanyl ($n = 22$)	52(12)	7/15	69(14)	96(7.2)	19 Cholecystectomy 2 Gastrectomy 1 Vagotomy
Placebo ($n = 18$)	47(12)	6/12	75(13)	100(8.7)	14 Cholecystectomy 1 Gastrectomy 3 Vagotomy

TABLE II. *Morphine demanded after surgery (mean (SEM)). (Student's* t *test)*

	Morphine requirement (mg)			
Group	90 min after surgery	First 24 h	Second 24 h	Total 48 h
Fentanyl	11.8(1.2)	32.5(3.3)	17.9(2.5)	49.9(4.9)
Placebo	16.3(1.1)	48.6(4.0)	28.4(3.2)	77.0(6.3)
P	< 0.01	< 0.01	< 0.05	< 0.01

TABLE III. *Median pain scores (ranges) (Mann–Whitney* U *test)*

Group	4 h	8 h	12 h	24 h
Fentanyl	4.5(0–9)	4.0(1–7)	3.0(0–8)	3.0(0–6)
Placebo	8.0(4–9)	6.0(3–9)	4.5(1–8)	5.0(1–7)
P	< 0.05	< 0.05	< 0.01	< 0.01

Arterial blood-gas tensions did not differ significantly (table V), but mean rates of ventilation were lower ($P < 0.05$) in the TTS-fentanyl group at 12 and 24 h (table VI). No patient was withdrawn from the study because of low ventilatory rates.

Mean (SEM) plasma fentanyl concentrations in the TTS-fentanyl group at 12 and 24 h were 1.5 (0.1) and 2.0 (0.2) ng ml^{-1}, respectively.

DISCUSSION

The TTS-fentanyl group demanded significantly less morphine in the first and second 24 h, but pain scores were consistently lower. Further evidence of improved analgesia in this group is shown by the greater PEFR. Rates of ventilation were lower in the TTS-fentanyl group at 12 and 24 h, but there were no differences in arterial blood-gas tensions. Although the placebo group demanded 33 % more morphine than the fentanyl group in the first 24 h, and had free access to morphine on demand, the quality of pain relief in the fentanyl group was significantly better.

TABLE IV. *(Mean (SEM)) peak expiratory flow rates as percentages of the preoperative value. (Student's* t *test)*

Group	8 h	12 h	24 h
Fentanyl	29(4.3)	41(4.2)	44(4.8)
Placebo	22(3.6)	25(2.5)	31(3.1)
P	ns	< 0.01	< 0.05

TABLE V. *Mean (SEM) arterial blood-gas tensions. No significant differences (Student's* t *test)*

	0 h	12 h	24 h
Fentanyl group			
Pa_{O_2} (kPa)	11.3(0.3)	8.7(0.2)	8.6(0.3)
Pa_{CO_2} (kPa)	5.1(0.1)	5.9(0.1)	5.9(0.1)
Placebo group			
Pa_{O_2} (kPa)	11.8(0.4)	8.7(0.2)	8.6(0.4)
Pa_{CO_2} (kPa)	5.0(0.1)	5.7(0.1)	5.5(0.1)

It is not clear why the placebo group did not demand more morphine. Greater analgesia in the TTS-fentanyl group may be explained by an inadequate on-demand morphine regimen, but this did not appear to be the case after the first 90 min of the study, as no patient demanded the maximum available dose of morphine. However, this probably was a factor during the immediate postoperative period, as two patients demanded the maximum available amount of morphine.

In a similar group of patients, the mean plasma half-life of fentanyl after removal of the patch was 15.7 h [7]. This is consistent with a depot of fentanyl remaining in the skin and may account for the fact that the TTS-fentanyl group demanded significantly less morphine in the 24 h after removal of the patch. The therapeutic range for plasma fentanyl concentration has been described as 1–3 ng ml^{-1} [11]. At 12 and 24 h, mean fentanyl concentrations in the TTS-fentanyl group were within this range (1.5 and 2.0 ng ml^{-1}).

Transdermal fentanyl resulted in better analgesia and PEFR associated with a reduction in morphine requirement after upper abdominal surgery. It may be useful in the management of postoperative pain. However, it seems likely that supplementary analgesia may be required in many patients if a system delivering fentanyl 100 µg h^{-1} is used. This was the maximum dose available at the time of the study.

In a previous study of similar design using fentanyl 100 µg h^{-1} i.v. for upper abdominal surgery [12], mean additional requirement for morphine was 19 (SEM 4) mg and pain was judged to be severe on 15 % of occasions. Direct comparison with this study is difficult, as pain in that study was assessed on a four-point scale at 8, 12 and 24 h only. No assessment was made in the immediate postoperative period and morphine was given i.m. as required. Furthermore, our previous study has shown that plasma concentrations of fentanyl in the early postoperative period were significantly greater during i.v. infusion compared with transdermal adminis-

TABLE VI. *Mean (SEM) rates of ventilation at times after application of the transdermal system. (Student's* t *test)*

Group	Before op.	4 h	8 h	12 h	24 h
Fentanyl	17.5(0.4)	16.8(0.7)	16.8(0.8)	15.7(0.9)	17.0(0.7)
Placebo	18.7(0.6)	19.4(1.2)	19.1(0.9)	18.3(0.7)	19.2(0.7)
P	ns	ns	ns	< 0.05	< 0.05

tration when administration commenced 2 h before surgery [7].

TTS-fentanyl provides a significant degree of background analgesia and this, combined with ease of administration, may be an advantage.

ACKNOWLEDGEMENTS

We are grateful to ALZA Corporation, Palo Alto, California, for providing the transdermal systems and for financial support.

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SUFENTANIL DISPOSITION IN PATIENTS UNDERGOING RENAL TRANSPLANTATION: INFLUENCE OF CHOICE OF KINETIC MODEL†

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There is controversy on the use of opioid drugs in patients with impaired renal function. Prolonged ventilatory depression and sedation have been reported following parenteral administration of morphine or papaveretum [1,2] and plasma concentrations of norpethidine, a metabolite with sedative and convulsant properties, increased when pethidine was given to patients with impaired renal function [3,4].

Studies on the elimination of sufentanil have shown that it has a high hepatic extraction ratio [5] with little involvement of the kidney in native drug clearance; hence the drug should be suitable for use in patients with both normal and impaired renal function. However, there have been reports of prolonged ventilatory depression with altered drug kinetics when sufentanil was given to renal transplant recipients [6,7]. The present study has therefore examined the disposition of sufentanil in such patients, and compared the kinetics with those from a comparable group of healthy anaesthetized patients undergoing lower abdominal surgery.

Studies of drug kinetics during anaesthesia show considerable variability [8,9]. In addition to clearly definable factors (patient age, fitness, choice of anaesthetic agents), different approaches to data handling may affect the estimates for clearance, volumes of distribution, and elimination half-life. Therefore the influence of the kinetic model on derived parameters has been examined also.

SUMMARY

We studied the disposition of sufentanil in 10 patients undergoing renal transplantation, and compared the data with those from eight healthy anaesthetized patients undergoing lower abdominal surgery. Patients received sufentanil 2.5 μg kg⁻¹ as part of a balanced anaesthetic technique. Central venous blood samples were collected at intervals up to 600 min, and plasma sufentanil concentrations assayed by radioimmunoassay. Pharmacokinetic parameters were calculated from drug concentration–time profiles by extended least squares non-linear regression analysis (ELSFIT) and by a model independent (MI) approach using AUC and its first moment, AUMC. There were no differences (based on MI results) between the two groups for elimination half-life ($T_{\frac{1}{2}}^{\beta}$) *(renal failure: 188 min; anaesthetized controls: 195 min), clearance* (Cl) *(1030 and 1093 ml min⁻¹) and apparent volume of distribution at steady state* (V^{ss}) *(223.0 and 215.3 litre). Sufentanil binding to plasma proteins was 91.4% in the renal patients and 92.2% in the healthy group (ns). Comparison of kinetic methods showed significant correlation of the individual estimates for* $T_{\frac{1}{2}}^{\beta}$, Cl *and* V^{ss} ($P < 0.01$)*. The mean absolute differences between methods were:* $T_{\frac{1}{2}}^{\beta}$ *2.7 min (95% limits: −26.2 to 31.5),* Cl *36.5 ml min⁻¹ (−5.5 to 78.4),* V^{ss} *−18.4 litre (−47.7 to 10.9). When the mean estimate for the two methods ((ELSFIT + MI)/2) was compared with the difference, there was no correlation for the estimates of* Cl *and* V^{ss}*. MI tended to overestimate clearance and underestimate volume of distribution. There was a significant relationship between estimates for elimination half-life, with a slope greater than zero.*

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†Presented in part at the Anaesthetic Research Society, Bristol Meeting, June 1988.

PATIENTS AND METHODS

Approval for the study was obtained from the local Hospital Ethics Committee, and all patients gave informed consent. Eighteen patients were studied (table I); 10 had chronic renal failure treated by haemodialysis, and were undergoing cadaveric ($n = 3$) or living related donor kidney transplantation through an extraperitoneal loin incision. None had received a previous renal transplant. Patients underwent renal dialysis within 6–16 h of transplantation, and maintained concurrent drug therapy up to and including the time of premedication. Patients in the healthy anaesthetized group were undergoing abdominal surgery. No patient in either group had clinical evidence of liver dysfunction or abnormal liver function tests. None of the 18 patients suffered significant intraoperative blood loss.

Premedication comprised diazepam 10 mg given by mouth 90 min before anaesthesia. Sleep was induced with thiopentone 3–4 mg kg^{-1} and the trachea intubated after vecuronium 0.1 mg kg^{-1} i.v. Anaesthesia was maintained with 60–67% nitrous oxide in oxygen and controlled ventilation adjusted to provide normocapnia. Volatile supplementation of anaesthesia was given only if patients showed clinical signs of inadequate anaesthesia (heart rate > 90 beat min^{-1}; arterial pressure $> 20\%$ greater than pre-induction value; sweating or lachrymation).

When stable anaesthesia had been achieved, sufentanil 2.5 µg kg^{-1} was administered i.v. over 30 s. After administration of the opioid, venous blood samples (5 ml) were taken into lithium–heparin tubes from a central venous catheter at times 0, 2, 5, 10, 15, 30, 45, 60, 90, 120, 180 min and then at additional times to 600 min.

At the end of surgery, residual neuromuscular block was antagonized with atropine 1.2 mg and neostigmine 2.5 mg. In those patients with ventilatory depression (< 10 b.p.m.; tidal volume less than 8 ml kg^{-1}), naloxone 0.2–0.4 mg was administered before tracheal extubation.

Throughout anaesthesia and surgery, heart rate and ECG were monitored continuously; arterial pressure was recorded non-invasively at 5-min intervals.

Sufentanil assay

Plasma sufentanil concentrations were measured using a radioimmunoassay with a sensitivity of 0.02 ng ml^{-1} [10]. This assay does not cross react with any of the known metabolites of sufentanil, with naloxone or with pethidine, which was given i.m. for postoperative analgesia. Plasma protein binding for sufentanil was determined by equilibrium dialysis at pH 7.4 and 37 °C against

TABLE I. *Details of patients in renal transplant group* (n = *10*) *and healthy anaesthetized group* (n = *8*). *RF = Renal failure*

	Age (yr)	Sex	Weight (kg)	Aetiology of RF/ surgical procedure	Concurrent drug therapy
Transplant					
1	54	F	66.0	Polycystic kidneys	None
2	39	F	50.0	Nephrotic syndrome	Atenolol; nifedipine
3	46	M	64.1	Obstructive uropathy	Atenolol; hydralazine
4	25	F	50.0	Chronic pyelonephritis	None
5	25	F	45.0	Polycystic kidneys	None
6	15	F	34.0	Chronic pyelonephritis	Metoprolol; nifedipine
7	30	F	53.0	Glomerulonephritis	None
8	39	M	68.6	Nephrotic syndrome	α-Methyl DOPA; amiodarone
9	30	M	53.2	Unknown; hypertension	Atenolol; hydralazine
10	33	M	61.3	Unknown; hypertension	Atenolol; minoxidil
Healthy					
1	59	F	60.8	Abdominal hysterectomy	
2	55	F	58.8	Abdominal hysterectomy	
3	57	F	65.9	Cholecystectomy	
4	62	F	54.4	Anterior resection	
5	37	F	58.8	Abdominal hysterectomy	
6	60	M	85.0	Ilio–femoral endarterectomy	
7	61	F	54.6	Cholecystectomy	
8	65	M	90.2	Anterior resection	

phosphate buffer 1 mol litre^{-1}. The coefficients of variation (intra- and inter-assay) were approximately 5% within the concentration ranges measured.

Other assays

Alpha$_1$-acid glycoprotein concentrations were determined using commercially available radioimmunodiffusion plates; plasma urea, creatinine, and serum albumin concentrations were measured by routine clinical laboratory methods.

Kinetic analysis of data

The plasma drug concentration–time curves for individual patients were analysed by two separate approaches. First, the data were analysed by a model-independent method (MI) with the area under the curve (AUC) and its first moment (AUMC) calculated using the linear trapezoidal method. The terminal or elimination half-life ($T_{\frac{1}{2}}^{\beta}$) was calculated by non-linear regression analysis and the following kinetic parameters derived: apparent volume of distribution at steady state (V^{ss}), plasma clearance (Cl) and mean residence time (MRT). Data were analysed also by extended non-linear least squares regression analysis (ELSFIT) with weighting proportional to the reciprocal of the variance of the measured drug concentration [11]. The suitability of the compartmental model chosen for each set of data (two- or three-compartment model) was based on evaluation of the residuals between measured and predicted plasma drug concentrations, and the maximum likelihood function.

Statistical analysis

Data are presented as the mean (SD) or range. Statistical significance between patient groups was determined using the Mann–Whitney *U* test. Kinetic parameters derived by the MI and ELSFIT analyses were compared using methods described by Bland and Altman [12].

TABLE II. *Pharmacokinetic variables determined by extended non-linear least squares regression analysis (ELSFIT) and model independent method (MI) in 10 patients with endstage renal failure undergoing transplantation, and eight healthy anaesthetized patients undergoing abdominal surgery, and sufentanil binding to plasma proteins at concentration of 0.5 ng ml^{-1} (mean values (SD)). MRT = Mean residence time; FF = free (unbound) fraction of sufentanil in plasma*

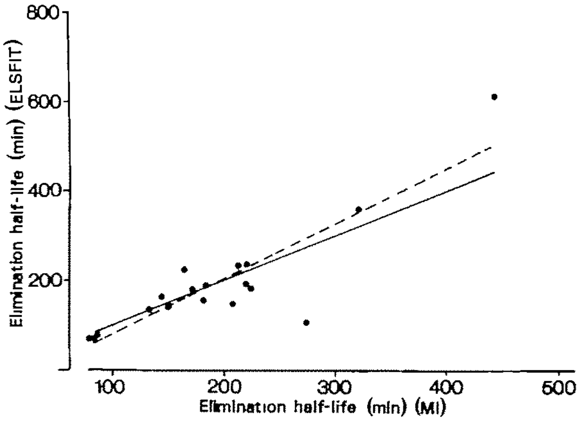
	ELSFIT analysis				MI analysis				
	$T_{\frac{1}{2}}^{\beta}$ (min)	MRT (min)	Cl (ml min^{-1})	V^{ss} (litre)	$T_{\frac{1}{2}}^{\beta}$ (min)	MRT (min)	Cl (ml min^{-1})	V^{ss} (litre)	FF (%)
Transplant									
1	80	87	1703	147.6	86	100	1710	170.6	8.0
2	228	161	555	89.5	162	141	563	79.4	5.8
3	178	186	859	160.3	172	185	830	153.0	8.0
4	148	139	845	117.6	207	201	804	163.4	8.3
5	163	159	720	114.2	143	163	609	99.4	9.9
6	74	75	852	63.8	81	88	820	72.0	10.4
7	190	178	1214	216.3	186	212	1097	232.7	9.5
8	153	144	1242	179.6	182	215	1100	236.4	7.6
9	190	185	1963	362.7	221	286	1742	497.5	9.2
10	608	635	950	605.1	437	528	1003	529.0	9.3
Mean	201	195	1090	205.7	188	212	1030	223.0	8.6
SD	151	159	446	163.4	99	125	410	163.0	1.3
Healthy									
1	106	91	1088	99.3	227	262	988	258.5	10.7
2	355	315	841	264.3	321	322	876	281.8	7.8
3	188	212	1015	215.9	223	233	1040	241.6	6.7
4	141	136	1371	186.5	133	134	1375	184.7	9.2
5	72	73	1887	137.9	80	79	1958	154.3	9.7
6	235	261	1020	266.1	214	206	871	179.4	5.9
7	238	220	666	146.1	218	229	726	165.9	5.8
8	147	150	1687	252.3	152	150	1710	256.1	6.3
Mean	185	182	1196	196.0	195	202	1093	215.3	7.8
SD	90	84	420	63.8	73	78	443	49.3	1.9

RESULTS

Anaesthesia was uneventful in all patients, and lasted 179.2 (37.6) min in the renal transplant group and 123.1 (43.2) min in the healthy patients. Preoperative plasma concentrations of urea and creatinine were 4.0 (1.1) mmol litre^{-1} and 92 (14) μmol litre^{-1} in the healthy patients; and 18.6 (10.5) mmol litre^{-1} and 714 (197) μmol litre^{-1} in the renal transplant patients ($P < 0.005$). In both groups, administration of sufentanil 2.5 μg kg^{-1} resulted in decreases in systemic arterial pressure (mean systolic pressure −25.3 %; mean diastolic pressure −29.0 %) and heart rate (mean −20.2 %). There were no differences between the groups, and all patients responded promptly to the infusion of crystalloid.

Mean concentrations of sufentanil at incision were 1.40 (0.58) ng ml^{-1} in the healthy anaesthetized group and 1.06 (0.75) ng ml^{-1} in the transplant patients (ns). No patient showed somatic or autonomic response to the surgical incision. During surgery, five of 10 patients in the transplant group and one of eight healthy anaesthetized patients received volatile supplementation of anaesthesia ($\leqslant 0.6\%$ enflurane) at plasma concentrations of sufentanil between 0.20 and 0.78 ng ml^{-1}. At the end of surgery, extubation of the trachea was achieved uneventfully in 15 of the 18 patients (plasma sufentanil concentration 0.05–0.51 ng ml^{-1}). Three patients in the healthy group received naloxone 0.2 mg i.v. to initiate adequate spontaneous ventilation. Plasma concentrations of sufentanil at tracheal extubation in these patients were 0.22–0.31 ng ml^{-1}.

Table II lists the derived parameters calculated by the two methods of kinetic modelling, with the percentage binding of sufentanil to plasma proteins at a drug concentration of 0.5 ng ml^{-1}. The free fraction of sufentanil did not differ between the two groups. No correlation was observed between the sufentanil free fraction or binding ratio (bound/free fraction) and the alpha$_1$-acid glycoprotein (α_1-AGP) concentration ($r = 0.318$ and 0.386, respectively). Concentrations of α_1-AGP were slightly greater in the renal failure group (1.25 (0.84) *v.* 0.89 (0.24) g litre^{-1}), although this did not achieve significance. Despite the increased concentrations of α_1-AGP



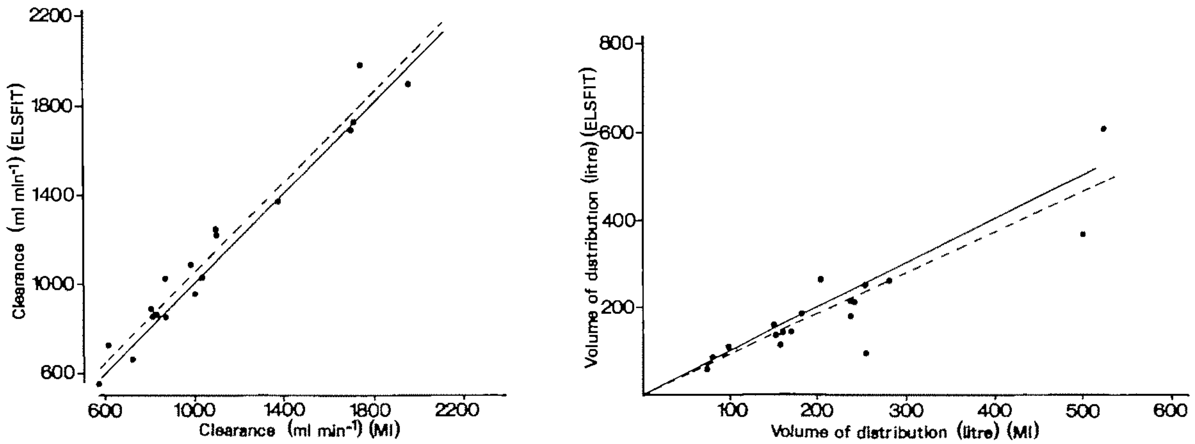


FIG. 1. Correction plots comparing elimination half-life ($T_{\frac{1}{2}}^{\beta}$), clearance (*Cl*) and apparent volume of distribution at steady state (V^{ss}) determined by model independent method (MI) and extended non-linear least squares regression analysis (ELSFIT) for 18 patients. —— = Regression line; - - - = line of identity. Regression equations: $T_{\frac{1}{2}}^{\beta}$: ELSFIT = 1.231MI−44.58; $r = 0.871$; $P < 0.01$. *Cl*: ELSFIT = 0.991MI+46.38; $r = 0.981$; $P < 0.01$. V^{ss}: ELSFIT = 0.921MI−2.34; $r = 0.897$; $P < 0.01$.

TABLE III. *Free drug kinetics for sufentanil in 10 patients with endstage renal failure undergoing transplantation and eight healthy patients undergoing abdominal surgery. Data calculated from ELSFIT kinetic parameters (table II) (mean (SD))*

	Cl_{free} (litre min^{-1})	V^{ss}_{free} (litre)
Renal patients	12.79 (5.14)	2366.2 (1704.8)
Healthy patients	15.75 (5.51)	2722.8 (1219.8)

in some patients in the renal transplant group, there was no correlation between α_1-AGP concentration and V^{ss} (total) for sufentanil. Serum albumin concentrations were similar in the two groups: 37.8 (4.3) and 41.7 (4.2) g litre^{-1}, respectively.

TABLE IV. *Mean absolute differences between kinetic parameters as calculated by ELSFIT and MI methods. Data shown as difference (ELSFIT–MI) and 95% confidence limits of the difference. MRT = Mean residence time*

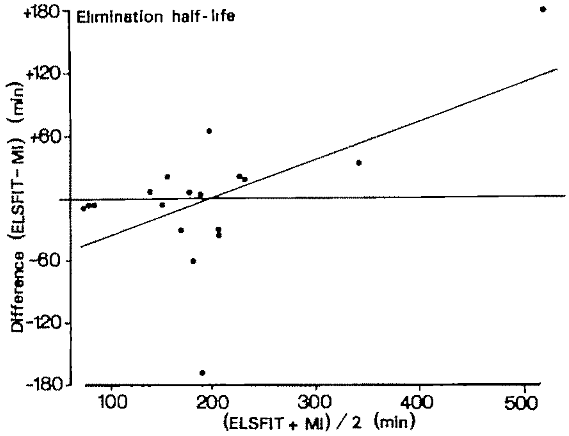
$T_{\frac{1}{2}}^{\beta}$ (min)	2.68 (−26.18 to 31.54)
Cl (ml min^{-1})	36.46 (−5.53 to 78.39)
MRT (min)	−18.02 (−47.41 to 11.37)
V^{ss} (litre)	−18.36 (−47.65 to 10.91)

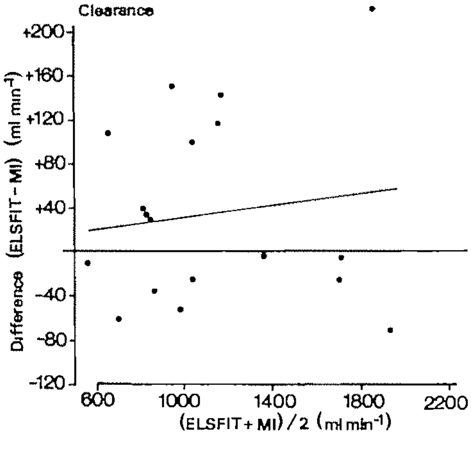
Kinetic values for elimination half-life, clearance, apparent volume of distribution at steady state and mean residence time were similar in both groups. Based on the parameter estimates determined from the total drug concentrations by the model-dependent method (ELSFIT), there were also no differences in free (unbound) drug clearance or free drug apparent volume of distribution at steady state between the two groups (table III).

As there were no significant differences in data for the two groups, these have been combined to allow comparison of the two methods of kinetic analysis (table IV).

Although there were differences between the calculated values for the three main kinetic parameters, none achieved statistical significance and the slopes of the MI *v.* ELSFIT plots (fig. 1) were not different from unity (the line of identity). This suggests good agreement between the two kinetic methods.

To examine if bias might exist between the two approaches, the difference between methods was compared with the average of the two methods (fig. 2). For all three parameters, there was wide dispersion of the values about the zero (ELSFIT–MI) intercept. For clearance and apparent volume of distribution, there was no





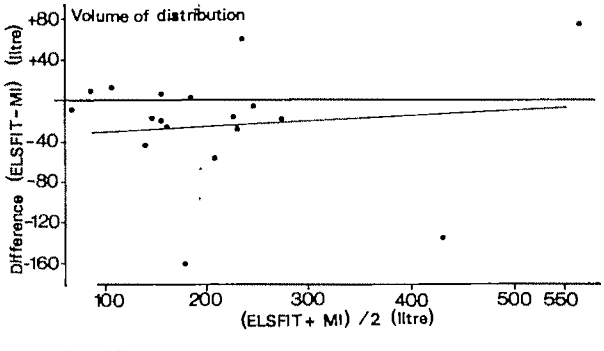


FIG. 2. Difference (ELSFIT−MI) [y] against mean value ((ELSFIT+MI)/2) [x] for elimination half-life, clearance and apparent volume of distribution at steady state for 18 patients. $T_{\frac{1}{2}}^{\beta}$: $y = 0.366x - 70.84$; $r = 0.583$; $P < 0.02$. Cl: $y = 0.028x - 25.64$; $r = 0.063$; ns. V^{ss}: $y = 0.025x + 7.39$; $r = 0.14$; ns.

significant correlation between average value and difference, and the slope of the correlation lines was not different from zero. MI kinetic methods resulted in an overestimation of clearance and underestimate of the apparent volume of distribution at steady state. This indicates fixed bias between the kinetic methods. For elimination half-life, a significant correlation was observed between the methods ($r = 0.583$; $P < 0.02$), with the slope significantly different from the zero (ELSFIT–MI) intercept, indicating a variable bias between the two kinetic methods. However, this correlation was influenced by a single data set.

DISCUSSION

In this study, the kinetics of sufentanil did not differ between healthy anaesthetized patients and those with chronic renal failure. This conflicts with the clinical report of Wiggum and colleagues [6]. Although polymorphic drug oxidation has been proposed as a mechanism for altered drug metabolism in some patients receiving alfentanil [13, 14], this is unproven, and there are no data to support such polymorphism for sufentanil metabolism. The variability of sufentanil clearance in the present study (37 %, $n = 18$) is similar to that cited for other opioids [8, 9, 15]. The range of sufentanil concentrations at tracheal extubation (0.05–0.51 ng ml^{-1}) was similar to those reported previously [16–18]. There were no apparent differences in the concentration–effect relationship between healthy anaesthetized patients and those with chronic renal failure.

Although other studies have investigated the influence of renal failure on disposition of sufentanil, there are few data from within-study, between-group comparisons. Differences in sampling times and sites, assay methodology and data analysis render comparisons between separate studies less than satisfactory. Data from most studies in the healthy anaesthetized patient have indicated an elimination half-life of 140–200 min [19–23]; thus the shortened sampling time (180 min) of Davis and colleagues [24] tended to underestimate half-life and overestimate clearance. In addition, Davis investigated adolescent subjects (aged 10–15 yr); the age range of the patients in the present study was 13–65 yr. Within our population there was no observed age-related influence on drug kinetics.

Renal failure alters the plasma protein binding of many drugs [25, 26]. For acidic compounds, there is frequently a decrease in binding, although the binding of basic drugs shows greater variability. Thus for the anilino–piperidine opioids, Bower found no influence of uraemia on the binding of fentanyl [27], while others reported an increase in the alfentanil free fraction [28, 29]. No effect of renal failure on sufentanil binding was seen in the present study, and hence no difference between patient groups in either free drug clearance or free drug apparent volume of distribution at steady state. It is unlikely, therefore, that chronic renal failure has a significant effect on drug dynamics.

In the present study, all transplanted kidneys showed immediate graft function. However, it is unlikely that this influenced significantly the disposition of drug in the renal failure group, as only 5–10 % of the parent drug is excreted unchanged via the kidney [5].

Sufentanil, in common with fentanyl and alfentanil, binds to α_1-AGP. However, there was no significant increase in the concentration of this acute phase protein in the patients with renal failure, and hence no relationship between the sufentanil free fraction and α_1-AGP.

There have been many observations on factors influencing drug disposition during anaesthesia [30, 31]. However, in comparing anaesthetic studies from healthy patients and those with renal failure or other diseases, little attention has been paid to the kinetic model from which parameters have been derived. The present data show no significant effect of the method of modelling on mean derived parameters. This is in agreement with other data [32, 33]. However, the wide 95 % confidence intervals of the means show the variation which may be introduced when comparing different methods.

Use of time-invariant mammillary modelling to define the behaviour of drug within a system depends on appropriate and adequate blood sampling to allow accurate derivation of the various micro-constants, in addition to presupposing the nature of drug distribution and metabolism. For any drug, distribution within the body may be considered in a number of different compartments. For a drug showing a biexponential decline in the concentration–time profile, a two-compartment kinetic model is assumed. There are, however, three possible and different models that may be defined for a given decay profile [34]. The advantages and inherent problems in compartmental modelling have been discussed elsewhere [35, 36].

Compartment independent analysis is a more robust method, as the parameter estimates are based on determination of the AUC and are therefore not sensitive to small fluctuations in the concentration–drug profile [37]; also there is an absence of need to define the various inter-compartmental rate constants, each dependent on the other, with progressively increasing errors and greater standard deviations [38]. These errors may be compensated for by use of advanced mathematical techniques, such as that described by Bower and Hull [39], but this involves significant computation. MI analysis is not dependent on such constraints, although one limitation of the method necessitates previous knowledge of the terminal rate constant (for calculation of the additional AUC and AUMC from the last data point to infinity), its calculation by the method of residuals (curve stripping), or its determination by linear regression analysis, with the analyst consigning the concentration–time point at which the terminal phase commences following visual inspection of the data.

Thus although there were only small differences between the mean parameter estimates calculated by the two kinetic methods, there was considerable variability when data were expressed as the 95 % limits. When data from separate studies are compared, use of different methods of data handling may increase inter-individual variability above that produced by other factors (age, fitness, disease states, etc.), and lead to erroneous conclusions. If adequate sampling regimens have been adopted and the correct kinetic model defined, the use of compartmental approaches may be preferred—otherwise, model independent analysis should be used to define drug disposition.

ACKNOWLEDGEMENT

The assistance of Dr J. Heykants and his colleagues, Department of Drug Metabolism, Janssen Pharmaceutica BV, Beerse, Belgium is acknowledged.

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Br. J. Anaesth. (1989), **63**, 68–75

EFFECTS OF TEMAZEPAM PREMEDICATION ON COGNITIVE RECOVERY FOLLOWING ALFENTANIL–PROPOFOL ANAESTHESIA

R. BAILIE, L. CHRISTMAS, N. PRICE, J. RESTALL, P. SIMPSON AND K. WESNES

Anaesthesia for day case surgery requires a technique which allows rapid recovery and a swift return to street fitness [1]. The i.v. induction agent propofol and the short acting opioid alfentanil have been shown to produce rapid recovery and minimal residual effects [2–5]. They would appear, therefore, to be ideally suited for day-case anaesthesia. However, recent attention has focused on the degree of preoperative anxiety in day-case patients and it has been suggested that temazepam, a short acting benzodiazepine, produces satisfactory anxiolysis without altering long term recovery [6].

A recent review of the literature identified no study which had used computerized assessments to measure cognitive recovery from anaesthesia. However, in a recent study with healthy volunteers, a series of microcomputerized cognitive tasks was able to measure a profile of cognitive decrements following hyoscine [7] which previous work had failed to identify. This suggests that computerization may increase greatly the sensitivity of cognitive assessment and may potentially identify effects of anaesthesia and premedication which have been overlooked previously. The present study was designed to use microcomputerized tasks to identify the degree of impairment in cognitive function on recovery from propofol–alfentanil anaesthesia and any additional effects of premedication with temazepam 20 mg.

SUMMARY

The effects of temazepam 20 mg and placebo were compared for premedication in patients anaesthetized with propofol and alfentanil and undergoing day surgery. Temazepam 20 mg significantly reduced preoperative anxiety and increased recovery time. A series of computerized cognitive tasks revealed significant deficits in attention and memory following anaesthesia, which were increased in range and magnitude by temazepam, which were apparent 30 min after surgery and had largely, but not completely, recovered at 4 h. This study has demonstrated that computerized cognitive testing can identify a wider profile of impairments produced by temazepam than has been found in previous work using non-computerized techniques.

PATIENTS AND METHODS

The patients studied were ASA I or II females, age 16–75 yr, scheduled for routine minor gynaecological surgery not involving tracheal intubation. Patients with significant cardiovascular disease, a history of allergy, or receiving therapy likely to modify the response to the agents used, were excluded from the study. All patients gave verbal consent to inclusion in the study.

On admission, all patients performed the cognitive tests, and completed the State and Trait scales of the State–Trait Anxiety Inventory (STAI [8]). The STAI was used as it has been found previously to be sensitive to the effects of temazepam as a premedication [9]. The Trait scale of the STAI gives a score which reflects the anxiety-proneness of the individual, while the State scale yields a score reflecting the level of anxiety of the individual at the time of completion

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of the scale. All the operations were performed during the morning of the day following admission. One hour before surgery, patients completed a further State scale and then received premedication. The hospital pharmacist, who was not involved in the study, had previously allocated them to one of two groups: group 1 received temazepam 20 mg orally and group 2 received an identical placebo capsule. All cognitive assessments were conducted by one of the authors (NP). No maximum number of patients was planned, as many as possible being recruited during a 5-month period. Because of a delay in obtaining matched placebo capsules, the first 26 of the 65 patients were allocated to group 1. This was unknown to the researcher undertaking the cognitive assessments and to those conducting the initial evaluation of data. All testing and initial evaluation of data was conducted double-blind.

On arrival in theatre, all patients completed a further questionnaire immediately before induction of anaesthesia. All anaesthetics were administered by the same anaesthetist (RB). Anaesthesia was induced with alfentanil 10 μg kg^{-1} i.v. followed by propofol 2 mg kg^{-1} and maintained with an infusion of propofol 12 mg kg^{-1} h^{-1} and alfentanil 0.5 μg kg^{-1} h^{-1}. All patients received 100% oxygen at a flow rate of 140 ml kg^{-1} via a Bain circuit. Apnoea of more than 90 s duration occurred following induction in 50% of patients, and was easily managed by manual ventilation. Apnoea did not extend after the end of surgery in any patient and no postoperative respiratory depression occurred. At the end of surgery the infusion was discontinued and the patients transferred to the recovery ward.

The time taken from the end of the infusion to the patient being able to give name, age and ward was recorded. The patients completed the cognitive tests 30 min after the end of the infusion and again 4 h after operation.

All patients were discharged from hospital on the day of operation when both anaesthetist and gynaecologist were satisfied with their condition.

Cognitive Test System

An automated microcomputer-based system for the assessment of drug effects on cognitive function has been developed [10, 11] and shown to have drug sensitivity in both laboratory settings with young volunteers [12] and applied settings with the elderly [13]. A version of the system which has been developed for use with mildly demented patients was the subject of a pilot study to determine its sensitivity in the recovery room [Wesnes, Simpson and Restall, unpublished data]. Twelve patients of both sexes (age range 19–69 yr) performed the tasks in a recovery room a few minutes after waking from a variety of surgical procedures. All were able to perform the tasks, but at a significantly lower level of efficiency than a control group of theatre staff. This pilot study indicated that the system was practical for use in this environment, and suggested that it was sensitive to residual impairments following anaesthesia. The Cognitive Drug Research Cognitive Assessment System, comprising a BBC Master Microcomputer, disk drive, colour monitor and response module, was used, therefore, in the present study. The software was written in BASIC with machine code subroutines included to permit response times to be recorded to the nearest millisecond. All information was presented via the monitor and all responses made by pressing one of two buttons on the response module.

The following tasks were used:

(a) Word recognition: A list of 12 words is presented on the monitor. Afterwards, these 12 words plus 12 new words are presented singly, and the patient indicates whether or not she recognizes each word by pressing either a YES or a NO button.

(b) Picture recognition: The procedure is the same as for word recognition, a series of 14 pictures being presented and 14 distractors included for forced choice recognition.

(c) Memory Scanning Task: A series of three digits is presented for the patient to remember, followed by a series of 18 digits. For each digit in the second series, the patient must identify whether or not it was in the original series and respond by pressing the YES/NO button.

(d) Number Vigilance Task: In this task, a digit is constantly displayed in the right hand side of the screen. A series of digits is displayed in the centre of the screen at a rate of 80 per minute, and the patient is required to press the response button when the digit in the centre matches that displayed on the right.

(e) Choice Reaction Task: Either the word NO or the word YES is presented on the screen and the volunteer has to press, as quickly as possible, either the button marked NO or that marked YES as appropriate. There are 20 trials.

The sequence of the stages of the test administration was:

Presentation of word list — 30 s
Immediate recognition testing of word list — 30 s
Presentation of picture sequence — 60 s
Number Vigilance Task — 75 s
Choice Reaction Task — 75 s
Memory Scanning — 45 s
Delayed recognition testing of word list — 30 s
Recognition testing of picture sequence — 60 s

The total time to complete the computerized tests varied between 10 and 15 min.

During the course of the trial, it was decided to introduce additional recognition testing to be completed by all new recruits. After the first postoperative performance of the tests, a further list of words and a series of pictures were presented and recognition testing was carried out on these immediately before the final test session.

Statistical analysis procedures

A test for normality [14] was used to determine the suitability of parametric analysis. Statistical comparisons between the groups were made with t tests if there were single data points per volunteer, or using planned t ratios [15] where repeated measures were made, as with performance measures. Split plot ANOVA, using the unweighted means solution because of the different sizes of the two groups, were conducted both on the complete set of the performance data and on difference from preoperative baseline scores. The planned t ratios utilized the appropriate error terms from the ANOVA. Where parametric analysis was not appropriate, Mann–Whitney and Wilcoxon testing was used.

RESULTS

Sixty-five patients entered the study and were given the opportunity to withdraw at any time. Six patients in the placebo group were withdrawn: three were too sleepy to perform the 30-min assessment, and three were not available for the 4-h assessment. Four patients in the temazepam group were withdrawn: two were not awake for the 30-min assessment, one was unwell 30 min after operation and one was not available for the 4-h assessment. No patient withdrew because of nausea or vomiting. Nineteen patients receiving placebo and 36 receiving active medication satisfactorily completed all stages of cognitive testing.

TABLE I. *Demographic data (mean (SD))*

	Placebo	Temazepam
Age (yr)	37.3 (12.8)	37.4 (9.3)
Weight (kg)	62.5 (10.3)	66.5 (13.1)

The two groups were matched for age and weight (table I). On admission, there was no significant difference between the two groups for either State or Trait scale scores of the STAI. The infusion times for the two groups were not significantly different (table II). The first postoperative assessment took place, on average, at 35.3 min (range 19–53 min) in the placebo group and 36.9 min (range 22–54 min) in the temazepam group. The second assessment took place, on average, at 243.7 (range 224–262) min in the placebo group and at 243.9 (range 234–268) min in the temazepam group. The two groups did not differ significantly in the times that these assessments were made.

Effects of temazepam on anxiety and immediate recovery

Figure 1 shows the effect of premedication on the anxiety levels measured using the State scale of the STAI. There was no difference between the groups before medication, whereas before induction the placebo group had a significantly higher level of anxiety than the temazepam group ($t(90) = 2.13, P < 0.05$). Further, testing over time indicated that the slight reduction in anxiety following temazepam was not significant, whereas the increase in anxiety in the placebo group was significant ($t(45) = 2.43$, $P < 0.02$).

TABLE II. *Infusion and recovery times (mean (SD)).* **Significant difference from placebo group ($P < 0.01$)

	Placebo	Temazepam
Infusion times (min)	7.3 (2.56)	9.7 (5.99)
Time to eye opening (min)	6.47 (2.52)	9.71 (6.0)**
Time to stating name, age, ward (min)	8.16 (2.65)	14.46 (5.46)**

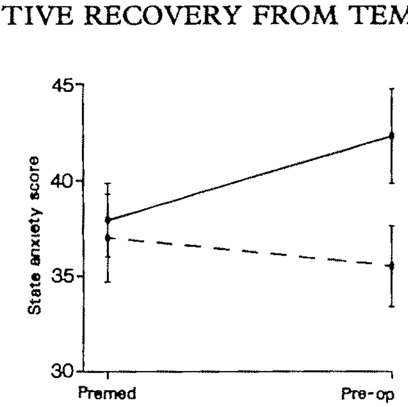

FIG. 1. Alleviation of preoperative anxiety by temazepam 20 mg (– – –) as assessed by the State Anxiety Scale of the State–Trait Anxiety Inventory. —— Placebo group. Mean (SEM bars).

Early recovery was significantly longer in the temazepam group, both in time to eye opening ($t(52) = 3.56$, $P < 0.01$) and in time to giving name, age and ward ($t(52) = 3.97$, $P < 0.01$) (table II).

Effects on cognitive function

Application of normality testing indicated normality of distribution for all data sets except for that of the accuracy of picture recognition (table III). Thus non-parametric statistical procedures were used only for this measure.

The effects of anaesthesia were evaluated by analysing the performance of the placebo group over time (table IV). At 30 min after surgery, significant decrements were found in the total number of pictures correctly identified, the speed of picture recognition, the speed of number matching and choice reaction time (figs 2–4). At 4 h after operation, only the speed of number matching was still impaired, although the accuracy of delayed recognition had decreased from the 30 min level, the only measure of any task in each group to do this.

In contrast, the temazepam group showed significant decline in all tasks in the speed of performance 30 min after operation, and decreases in the numbers of items identified correctly in the verbal and picture tasks. These impairments were highly significant (table IV).

Comparing the two groups at 30 min, the temazepam group performed consistently worse than placebo (table V). They were significantly slower at number matching, choice reaction, memory scanning, immediate verbal recognition and delayed verbal recognition. Significant impairments were found also in the total number of items recognized correctly on immediate verbal recognition and picture recognition. The impairments in accuracy of delayed verbal recognition and the speed of picture recognition just failed to reach statistical significance ($P < 0.1$). None of these differences was significant at the 4-h postoperative assessment.

An additional test was performed by 15 patients

TABLE III. *Means (SD) of the measures from the computerized cognitive tasks*

	Placebo (n = 19)			Temazepam (n = 36)		
Measure	Pre-dose	30 min	4 h	Pre-dose	30 min	4 h
Immediate verbal recognition						
Number correct (total = 24)	21.53 (1.3)	20.74 (2.6)	21.47 (1.9)	21.78 (1.4)	19.19 (2.3)	20.64 (1.9)
Speed (ms)	811.8 (385)	798.9 (190)	688.2 (126)	784.7 (191)	1013.8 (293)	773.0 (200)
Delayed verbal recognition						
Number correct (total = 24)	21.21 (2.4)	20.89 (1.7)	19.37 (3.2)	20.39 (1.9)	18.75 (2.5)	18.86 (2.0)
Speed (ms)	854.5 (338)	837.9 (228)	773.5 (165)	866.1 (230)	1021.9 (254)	851.6 (133)
Picture recognition						
Number correct (total = 28)	26.58 (2.0)	25.05 (2.1)	26.05 (1.9)	26.89 (1.2)	23.31 (3.4)	25.92 (2.2)
Speed (ms)	723.5 (136)	827.6 (176)	745.2 (136)	736.1 (116)	916.7 (249)	778.2 (157)
Number matching						
Speed (ms)	368.4 (56)	434.8 (87)	404.1 (51)	362.4 (47)	460.9 (69)	405.9 (57)
Choice reaction						
Speed (ms)	411.7 (57)	460.1 (78)	433.9 (60)	410.6 (45)	498.3 (100)	444.8 (60)
Memory scanning						
Speed (ms)	606.7 (114)	608.2 (119)	586.6 (118)	605.6 (139)	704.2 (157)	629.1 (124)

TABLE IV. *Significant impairments in performance compared with baseline*

	Placebo		Temazepam	
Measure	Time	*P* (df = 106)	Time	*P* (df = 106)
Immediate verbal recognition				
Accuracy			30 min	< 0.001
Speed			30 min	< 0.001
Delayed verbal recognition				
Accuracy			30 min	< 0.01
	4 h	< 0.01	4 h	< 0.01
Speed			30 min	< 0.01
Picture recognition				
Accuracy	30 min	<0.0097	30 min	< 0.00001
			4 h	< 0.0055
Speed	30 min	< 0.01	30 min	< 0.001
Number matching				
Speed	30 min	< 0.0001	30 min	< 0.0001
	4 h	< 0.01	4 h	< 0.01
Choice reaction				
Speed	30 min	< 0.01	30 min	< 0.001
Memory scanning				
Speed			30 min	< 0.001

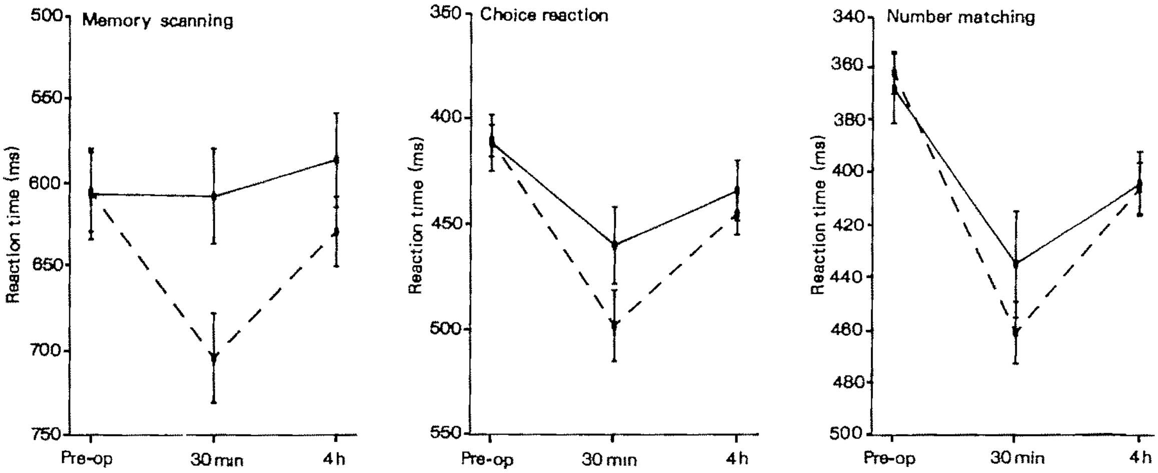

FIG. 2. Cognitive effects of anaesthesia, with (---) or without (—) temazepam premedication. Speed of performance of tasks involving differing levels of information processing (means and SEM bars).

in the temazepam group and 20 in the placebo group. This measured their ability, 4 h after operation, to recognize information presented 40 min after operation. Both groups performed only minimally above chance levels for verbal recognition and, while performance on the picture recognition task was better, it was considerably inferior to performance at 30 min after operation. However, there were no significant differences between the groups in any of these scores.

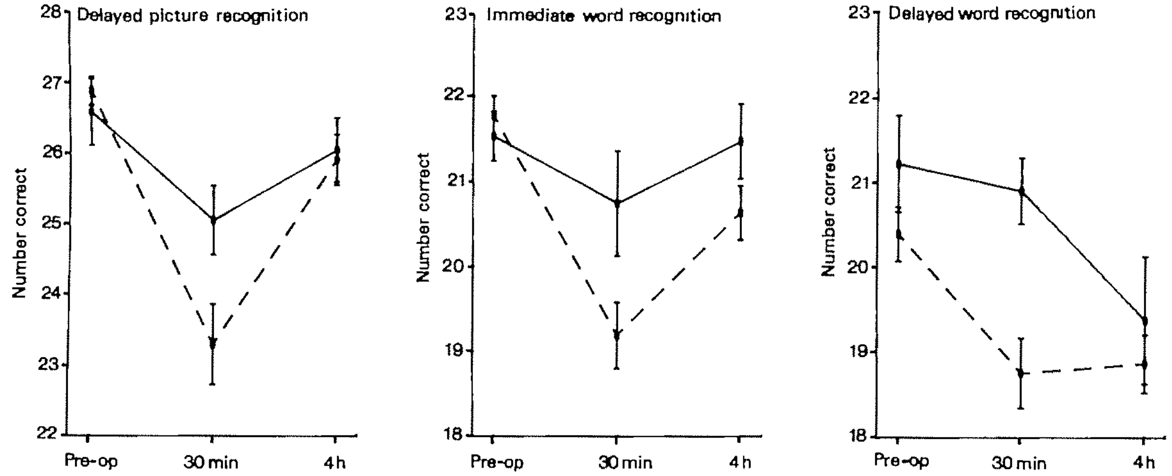

FIG. 3. Cognitive effects of anaesthesia, with (– – –) or without (—) temazepam premedication. Accuracy of recognition memory performance (means and SEM bars).

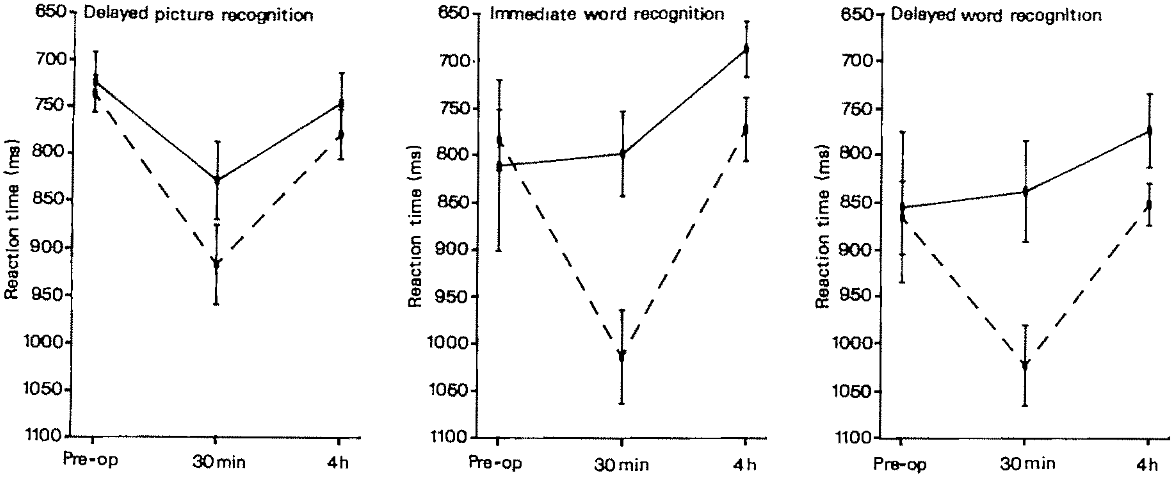

FIG. 4. Cognitive effects of anaesthesia, with (– – –) or without (—) temazepam premedication. Speed of recognition memory performance (means and SEM bars).

Relationship between infusion time and time to eye opening

The time of infusion was correlated with the early waking times. For the placebo group significant negative correlations were found between infusion times and both time to eyes open ($r = -0.49$, df $= 18$, $P < 0.05$) and time to state name, age and ward ($r = -0.46$, df $= 18$, $P <$ 0.05). For the temazepam group, the corresponding coefficients were $r = -0.26$ (df $= 33$, $P < 0.1$) and $r = -0.05$, respectively.

Although the difference in the average duration of infusion time for the placebo and temazepam groups (7.3 and 9.7 min, respectively) was not significant, it was decided to investigate its relevance. The difference was the result, not of a general trend but, as an inspection of the data indicated, of a few volunteers in the temazepam group having longer infusion durations than was typical. Removal of the six temazepam patients who had longer operation times than any in the placebo group decreased the average for the group to 7.48 min. It was decided to determine if the

TABLE V. *Significant impairments and trends induced by temazepam premedication, in addition to those induced by anaesthesia alone*

Measure	Time	P (df = 53)
Immediate verbal recognition		
Accuracy	30 min	< 0.01
Speed	30 min	< 0.01
Delayed verbal recognition		
Accuracy	30 min	< 0.1
Speed	30 min	< 0.02
Picture recognition		
Accuracy	30 min	< 0.0034
Speed	30 min	< 0.1
Number matching		
Speed	30 min	< 0.02
Choice reaction		
Speed	30 min	< 0.05
Memory scanning		
Speed	30 min	< 0.01

pattern of the results had been influenced by the inclusion of these six patients. Their data were removed and a number of parameters re-examined. Time to eyes open was unaffected (11.8 min for the 29 volunteers compared with 11.5 min for the whole group), as was time to state name, age and ward (13.45 min, compared with 13.48 min when the six patients were excluded). Finally, the cognitive data were re-analysed with the six patients excluded, but an identical pattern of changes both between and within the groups was detected. It is safe to conclude that the inclusion of the patients with the longer induction times has no bearing on the outcome of the study results and does not warrant their exclusion from the analysis.

DISCUSSION

This study has shown that anaesthesia produced a clear pattern of cognitive decrements which was more extensive when temazepam 20 mg was given as premedication. At 30 min after anaesthesia, information processing was impaired, as indicated both in the increased time to detect the targets in the number matching task, representing decreased vigilance, and the slowing of choice reaction performance, representing slowing of the processing of the stimuli and the selection of relevant responses. Impaired memory was seen in the decreases in the speed and accuracy of object recognition. At 4 h after operation these impairments were reduced by varying amounts, performance on several measures returning to the preoperative levels. However, in the absence of a control group and an opportunity to conduct practice sessions on the tasks, it is not possible to specify whether these apparent recoveries by 4 h were solely a recovery from drug-induced impairments or were partially the result of improvement in efficiency resulting from repeated performance on the tasks. Nonetheless, performance on two tasks did not recover by 4 h (speed of vigilance and accuracy of delayed verbal recognition).

A further effect detected was the failure of both groups to show long term verbal learning for the words presented at 40 min after operation. The inclusion of this testing in a subset of patients was made because of the frequently observed phenomenon that, soon after surgery, patients may answer questions and appear coherent and alert, but later they deny any knowledge of the episode. Clear evidence of verbal learning was evident at 30 min after operation, delayed verbal recognition being at the same level as immediate recognition for both groups at this time, indicating that such information could be maintained over a 7–10 min period. Thus anaesthesia appeared to produce a selective "long term" anterograde amnesia which was not indicated over an "intermediate term", and consequently reflected a failure to store or retrieve information rather than a failure to attend to or to register the information. A practical implication of this is that any precautionary information (e.g. avoiding driving) which is given during the immediate postoperative period is unlikely to be retained.

Temazepam significantly affected performance in all the tasks, either by increasing the decrements following anaesthesia at 30 min, or by impairing aspects of performance which were unaffected by anaesthesia at this time. At 4 h the effects of temazepam could no longer be differentiated from those of placebo. In considering the differences detected between the two groups, the lack of initial randomization must be acknowledged. However, this did not affect the double-blind nature of the trial.

Previously, impairments following premedication with temazepam 20 mg have been found in the accuracy of delayed recall [6] but have not been found for performance on the Digit Symbol Substitution task [16] or for reaction time [17]. Further, temazepam 20 mg given without anaesthesia only affected performance on the Digit Symbol Substitution task at 30 min after administration; letter cancellation and pursuit rotor were unaffected at this and later assessments [18]. Therefore, as would be expected from previous work [7], the findings of the present study indicate that computerized testing can detect a greater profile of effects with temazepam than has been obtained with traditional assessment methods.

The increased time to open eyes following temazepam 20 mg has been found in some previous studies [6, 17], but not others [16, 19]; the reasons for this disparity are not clear. An interesting and unexpected finding of the present study was the negative correlation between wake up time and duration of anaesthesia in the placebo group.

The alleviation of preoperative anxiety assessed by the Spielberger questionnaire is in accordance with similar effects of temazepam which have been detected using visual analogue scale techniques [6, 16, 19, 20], indicating that both techniques are sensitive to these effects.

Overall, the findings of this study are consistent with previous work, in that temazepam 20 mg produces anxiolysis before operation at the expense of longer times to opening eyes and impaired cognition 30 min later. The general recovery of these cognitive impairments by 4 h suggests that the drug is suitable for day-case surgery. However, the residual decrease in vigilance in both groups at 4 h indicates that patients have not recovered completely by this time.

ACKNOWLEDGEMENTS

The study was supported financially by Cognitive Drug Research who also provided the software, equipment and personnel for conducting the cognitive assessments.

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Br. J. Anaesth. (1989), **63**, 76–80

PRODUCTION OF LAUDANOSINE FOLLOWING INFUSION OF ATRACURIUM IN MAN AND ITS EFFECTS ON AWAKENING

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AND D. P. CRANKSHAW

SUMMARY

Twenty patients were given maximal doses of atracurium or vecuronium by infusion during surgery. Anaesthesia was maintained with an infusion of thiopentone, nitrous oxide and fentanyl. In patients administered atracurium, the plasma laudanosine concentration at cessation of surgery was 0.34 (SD 0.22) μg ml⁻¹; there was little tendency to cumulate during operation. A 20% higher arterial concentration of thiopentone was found at awakening in patients given atracurium, suggesting CNS stimulation by laudanosine, although the effect is too modest to be of clinical significance.

The continuous infusion of a neuromuscular blocking drug provides a flexible method for maintaining adequate muscle relaxation during surgery, and is particularly suited to atracurium. Its short elimination half-life (20 min) and limited volume of distribution allow a stable infusion rate to be attained within the first 30 min after the start of infusion while ensuring prompt spontaneous recovery when the infusion is discontinued [1,2]. However, there is concern on the possible accumulation of laudanosine, a major metabolite of atracurium, because of its significantly longer elimination half-life (220 min) [1,3].

Laudanosine has been shown to induce epileptiform activity in plasma concentrations of 5 μg ml^{-1} (healthy rabbits [4]) and 17 μg ml^{-1} (healthy dogs [5]), but concentrations up to 100 μg ml^{-1} do not induce epileptiform activity in cats [6]. This large interspecies variation makes it impossible to make extrapolation to man. However, following a study in rabbits in which laudanosine 0.5–0.9 μg ml^{-1} produced a 30% increase in the MAC for halothane, Shi and colleagues concluded that "if these data apply to humans, the incidence of awareness in lightly anaesthetized patients may be increased during the administration of atracurium" [7].

The aims of this study were to determine the plasma concentrations of laudanosine resulting from infusion of maximal clinical doses of atracurium during anaesthesia in man and to determine if central nervous system (CNS) stimulation can be detected under these conditions.

PATIENTS AND METHODS

We studied 20 adult patients undergoing major orthopaedic or vascular surgery. The patients gave informed consent and the study was approved by the Board of Medical Research of The Royal Melbourne Hospital. The patients had no clinical or biochemical evidence of hepatic, renal or neurological disease. A standard anaesthetic technique was used. Each patient was premedicated 1 h before surgery with temazepam 5–10 mg by mouth. Anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and fentanyl 1–3 μg kg^{-1} and maintained with a continuous infusion of thiopentone and 70% nitrous oxide in oxygen. Incremental doses of fentanyl, to a maximum dose of 0.5 μg kg^{-1} h^{-1}, were administered as necessary by the responsible anaesthetist, but none was

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Accepted for Publication: January 5, 1989.

administered in the 30 min before the end of surgery. The infusion was designed to maintain a constant arterial plasma concentration of thiopentone 10 μg ml^{-1} with a variable rate infusion profile based on the concept of Plasma Drug Efflux [8].

The 20 patients were allocated to pairs according to the neuromuscular blocking drug used. The patients were matched according to sex, age and expected duration of the surgical procedure, with the initial patient of each pair allocated randomly to receive either atracurium or vecuronium. Muscle paralysis was monitored following stimulation of the ulnar nerve at the wrist via cutaneous electrodes with a peripheral nerve stimulator (Bard Biomedical Peripheral Nerve Stimulator model 750 digital, Billerica, Ma, U.S.A.) with manual evaluation of the response of adductor pollicis. An initial bolus dose of either atracurium 0.5 mg kg^{-1} or vecuronium 0.1 mg kg^{-1} was administered to facilitate tracheal intubation, and intense muscle paralysis was maintained with a variable rate infusion adjusted to maintain a post-tetanic count of 1–3 (the number of responses to 1 Hz stimulation 3 s after a 50-Hz tetanus for 5 s) [9].

Controlled ventilation was adjusted to maintain normal blood-gas tensions and acid–base status. Nasopharyngeal temperature was maintained greater than 35 °C.

The infusion of neuromuscular blocking drug was stopped 10–15 min before the anticipated cessation of surgery. The residual neuromuscular block was antagonized with neostigmine 0.035 mg kg^{-1} and atropine 0.015 mg kg^{-1} when there were two or more responses to train-of-four (TOF) stimulation. On completion of surgery and when there was no fade to TOF stimulation, the thiopentone infusion was stopped and the patient's lungs ventilated with 100% oxygen. Each patient was asked by name at 30-s intervals to open the eyes. A response was taken as positive when the patient opened the eyes 2 mm or more. The trachea was then extubated and the patient transferred to the recovery room.

Arterial blood samples were taken for drug analysis from a radial artery cannula at cessation of the thiopentone infusion, when the patient opened eyes to command, and in the recovery room. The samples were immediately acidified to prevent continued breakdown of atracurium to laudanosine, centrifuged and the plasma frozen for later analysis. In five patients who received atracurium, arterial blood samples were taken every 30 min during the procedure to determine the intraoperative time course of plasma laudanosine concentration.

The total plasma concentrations of thiopentone and of laudanosine were measured by high pressure liquid chromatography. A reverse-phase system was used for thiopentone, with a 10-μm octadecylsilane column and mobile phase of 52% methanol, 43.5% water and 4.5% isopropanol at pH 3.5 [8]. This assay was sensitive to a thiopentone concentration of 20 ng ml^{-1} with a coefficient of variation of 1% at 12 μg ml^{-1}. A 5-μm silica column was used for laudanosine, with a mobile phase of 50% acetonitrile in sulphuric acid 0.0001 mol $litre^{-1}$, with the assay sensitive to a laudanosine concentration of 20 ng ml^{-1} and a co-efficient of variation of 2.8% at 5 μg ml^{-1}.

All patients were interviewed after operation. They were asked specifically for the last thing remembered before going to sleep, the first thing remembered on awakening and recall of anything during the procedure, including dreams.

The results are presented as mean values (SD). Comparison between means was performed using Student's *t* test for unpaired samples. Linear regression and correlation were calculated by the least square method, and assessed by analysis of variance. A probability level of $P < 0.05$ was considered significant.

RESULTS

The groups administered atracurium or vecuronium were similar with regard to patient parameters, anaesthetic drug dose, and arterial thiopentone concentrations at cessation of the infusion (*t* test, ns) (table I). The mean dose of vecuronium was 0.17 (0.02) mg kg^{-1} h^{-1} and atracurium 0.70 (0.04) mg kg^{-1} h^{-1}.

TABLE I. *Patient details and anaesthetic drug doses (mean (SD))*

	Vecuronium group	Atracurium group
Age (yr)	64 (16)	62 (18)
Weight (kg)	65 (12)	69 (8)
Thiopentone dose (mg kg^{-1})	17.5 (3.5)	20.1 (4.8)
Thiopentone concentration end infusion (μg ml^{-1})	7.23 (2.02)	8.28 (1.70)
Fentanyl dose (μg kg^{-1})	3.32 (0.77)	2.78 (1.21)
Duration of infusion (min)	163 (41)	189 (63)

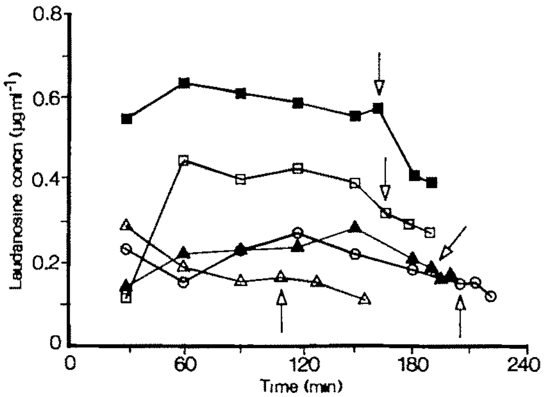

FIG. 1. The intraoperative and immediate postoperative arterial concentration of laudanosine in five patients administered atracurium by infusion. Atracurium was infused to maintain a post-tetanic count of 1–3. Arrows indicate cessation of surgery.

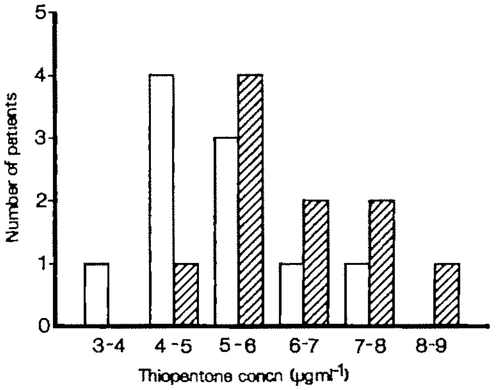

FIG. 3. Distribution of thiopentone concentration at awakening in the patients administered atracurium (hatched bars) and vecuronium (open bars).

The arterial plasma concentration of laudanosine during and following infusion of atracurium in five patients is illustrated in figure 1. At cessation of surgery, the arterial plasma concentration of laudanosine was 0.34 (0.22) µg ml^{-1} (range 0.07–0.81 µg ml^{-1}) in the 10 patients who received atracurium. This concentration was related significantly to the total dose and mean infusion rate of atracurium (fig. 2). Normalization of the dose and infusion rate to the patient's weight abolished the relationship.

The time from cessation of the thiopentone infusion until patients opened their eyes 2 mm or more on command was similar for patients administered atracurium and vecuronium (9 (7) min *v.* 10 (7) min, ns). However, patients administered atracurium had a 20 % higher mean arterial concentration of thiopentone (6.12 (1.16) µg ml^{-1} *v.* 5.12 (1.20) µg ml^{-1}; *t* test, $P < 0.05$) at awakening (fig. 3).

Postoperative interviews elicited no evidence of awareness or dreams in any patient.

No significant correlation was found between the total dose of thiopentone and the plasma concentration of thiopentone when patients opened eyes on command (vecuronium group $r = 0.01$, atracurium group $r = 0.49$; $n = 10$, ns), or between the arterial plasma concentration of laudanosine and the plasma concentration of thiopentone when patients opened eyes to command ($r = -0.53$, $n = 10$, ns).

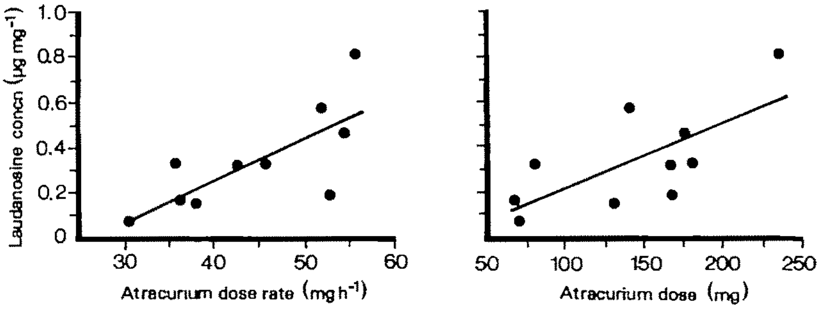

FIG. 2. Relationship between arterial plasma concentration of laudanosine at cessation of surgery and mean rate of administration of atracurium and the total dose of atracurium. Left: With mean rate of administration of atracurium, laudanosine (µg ml^{-1}) = 0.018 × administration rate (mg h^{-1}) − 0.47; $r = 0.74$, $n = 10$. Right: With total dose of atracurium, laudanosine (µg ml^{-1}) = 0.0029 × dose (mg) − 0.06; $r = 0.70$, $n = 10$.

DISCUSSION

The post-tetanic count allows assessment of profound peripheral muscle paralysis [7]. Such paralysis may be required occasionally during surgery because of the varying sensitivity of different muscle groups to neuromuscular blocking drugs. The diaphragm may not be paralysed at a time of apparent total paralysis of the peripheral muscles [10]. The maintenance of a post-tetanic count of 1–3 during surgery required a mean infusion rate of atracurium 0.7 mg kg^{-1} h^{-1} and should represent the maximal clinical infusion rate for atracurium. This infusion rate compares with a previously reported infusion rate of atracurium 0.4 mg kg^{-1} h^{-1} to achieve neuromuscular blockade during intra-abdominal surgery [11].

The plasma laudanosine concentrations following infusion of atracurium in this study were highly variable for 105–303 min, but similar to the peak values reported following single bolus doses of atracurium [12]. This is in contrast to prolonged infusions of atracurium in intensive care patients in whom peak concentrations of laudanosine as great as 5.1 μg ml^{-1} have been reported [13].

The infusion of atracurium during surgery did not appear to result in a tendency for the plasma concentration of laudanosine to increase, in contrast to pharmacokinetic predictions based on single bolus dose data. A steady state plasma concentration of laudanosine 1 μg ml^{-1} would be expected to be produced by an atracurium infusion of 0.6 mg kg^{-1} h^{-1} [1]. The failure of the plasma laudanosine concentration to increase early in the infusion may result from continuing distribution of laudanosine to fat and other tissues, as laudanosine is a highly lipophilic tertiary amine with a large volume of distribution [14].

The higher arterial plasma concentration of thiopentone at awakening in patients who received atracurium suggests that laudanosine, in concentrations that occur in surgical patients, may have a small but detectable CNS stimulatory effect. The intensity of effect corresponds to the 20–30 % increase in the MAC of halothane found in rabbits with similar plasma concentrations of laudanosine [7]. Using opening of eyes on command as a criterion, awakening from anaesthesia has previously been found to occur at a relatively constant alveolar concentration for several of the volatile anaesthetic agents [15] and of thiopentone following infusion anaesthesia [16]. Eye opening on command may be considered an all-or-none response and does not require a blind observer for accurate assessment. Pain resulting from the surgery does not appear to be an important stimulus for awakening in the period immediately after operation [15]. Residual effects of nitrous oxide are unlikely to have influenced the observation in this study, as the time from discontinuation to responding was similar in the two groups.

The clinical significance of the stimulatory effect of laudanosine is difficult to determine as it was only modest, such that the mean concentration of thiopentone at awakening of patients who received atracurium was still within 1 SD of that of control patients who received vecuronium. The stimulant effect of laudanosine would be expected to hasten recovery from anaesthesia in patients administered atracurium and to cause these patients to be more alert in the immediate postoperative period. However, in this study there was no difference in the time to recovery from anaesthesia, although this may have been masked by the slightly greater plasma concentration of thiopentone at cessation of surgery in the atracurium group.

Although the vencuronium group received a greater (but not significantly so) mean dose of fentanyl than the atracurium group, the dose regimen of fentanyl was restricted to very small amounts in all patients, to ensure low plasma concentrations in all patients at awakening. Fentanyl has a shallow dose–response curve [17], so small variations in individual doses should not have a significant effect on the thiopentone concentration at which patients awaken.

Acute tolerance to thiopentone was not observed in this study. This is in agreement with a previous infusion study of thiopentone [12] and the consistent EEG changes with three successive short term infusions of thiopentone [18]. Venous sampling following a single dose is the probable reason for the suggestion in previous studies that acute tolerance to thiopentone occurs in man [19]. Because of the longer sleeping time, a larger dose of thiopentone has longer to diffuse into muscle and fat, allowing a higher venous concentration at awakening as the concentration gradient between arterial blood and tissues decreases, with less extraction of thiopentone at awakening than for a smaller dose [20].

The lack of relationship between the arterial concentration of laudanosine and the thiopentone concentration at awakening suggests that there may be a ceiling effect to the stimulatory effects of laudanosine. Shi and colleagues have suggested previously [7] that there may be a ceiling effect to the increase in the MAC of halothane produced by laudanosine in rabbits.

ACKNOWLEDGEMENTS

This work was supported in part by the National Health & Medical Research Council of Australia (Grants 840680 and 830810) and Wellcome Australia Limited.

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Br. J. Anaesth. (1989), **63**, 81–86

COMPARISON OF I.V. SEDATION WITH MIDAZOLAM AND INHALATION SEDATION WITH ISOFLURANE IN DENTAL OUTPATIENTS

G. D. PARBROOK, D. M. STILL AND E. O. PARBROOK

SUMMARY

I.v. midazolam was compared with inhalation sedation using isoflurane in 80 dental outpatients. Preoperative anxiety was comparable in both groups and decreased after operation to similar values. The dental surgeon and the patients rated the techniques as equally satisfactory. Midazolam produced faster induction of sedation ($P < 0.001$) and more amnesia for the injection of local analgesic ($P < 0.001$), whereas isoflurane produced more euphoria ($P < 0.01$) and quicker recovery ($P < 0.001$). The incidence of postoperative side effects was similar in the two groups.

Midazolam is an established i.v. agent for sedation of dental outpatients [1], with nitrous oxide as an alternative inhalation technique [2]. Nitrous oxide has a considerable safety margin as it avoids the danger of greater degrees of sedation, but its lack of potency is a disadvantage in resistant patients, and there is a possible health risk to staff from trace quantities of the agent released into the dental surgery [3].

Sedation with isoflurane may have some advantages over nitrous oxide sedation, in that it retains a reserve of potency [4–6] and so gives smoother control of sedation. It has also shown some promise as an alternative sedative to midazolam in the critically ill [7]. We have therefore compared isoflurane and midazolam for dental outpatient sedation. A blinded trial was impossible as the two techniques were so different and because it was essential that the user retained the option of adjusting the dose of sedative to the need of the individual patient.

PATIENTS AND METHODS

Ethics Committee approval was obtained. The patients had been referred for oral surgical procedures and required sedation because of anxiety, some having a history of failure of treatment without sedation. Patients with a serious medical disease, receiving regular psychotropic drugs or with mask phobia were excluded from the trial. Exclusion was not thought likely to bias the results, as the eight patients excluded presented clear contraindications. To keep an approximate balance of the numbers of each sex treated, the two techniques were used alternatively in male and in female patients. The same anaesthetist (G.D.P.) administered sedation in all cases. Patients were instructed to have a light breakfast on the day of treatment and to arrange to have an escort home. All treatments were given in the morning. Informed written consent was obtained, followed by a medical history and clinical assessment. Anxiety was assessed using the Corah dental anxiety scale [8] and a 10-cm visual analogue scale. Co-ordination was tested with a board on which the patient tapped target areas with a stylus for 10 s [9].

The dental chair was adjusted so that the back was at an angle of 25° to the horizontal. ECG electrodes and a pulse oximeter were applied to the patient and arterial pressure was measured by oscillotonometry.

Midazolam 1 mg ml^{-1} was given via a cannula in a vein in the hand. An initial dose of 2.5 mg was followed by supplements of not more than 1 mg per minute until sedation was judged adequate. At

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this point local analgesic was injected by the dental surgeon. Verrill's sign of ptosis [10] was often present, but was not used as a guide because many patients preferred to close the eyes voluntarily during initial induction of sedation. Its presence or absence was noted when the patients opened the eyes during conversation during operation.

In the isoflurane group oxygen 7 litre min^{-1} passed through a prototype 0.2–1.4% Penlon vaporizer to a reservoir bag and Dupaco nasal mask. The patient was familiarized with the mask and nasal breathing technique with oxygen alone, then isoflurane was introduced in a concentration of 0.2% and increased by 0.1% each 30s to 0.6%, the concentration thereafter being increased or decreased until sedation was judged adequate.

Heart rate and pulse oximeter readings (Sa_{O_2}) were noted at 5-min intervals. The dose of midazolam and concentration of isoflurane were also noted, as was the time at which local analgesic was injected. After treatment the dental chair was returned to the sitting position and after 2 min the patient was transferred by chair to a couch in the recovery area. The dental surgeon completed a form giving his clinical assessment after the surgery.

Immediately after operation the patient's heart rate and arterial pressure were measured and patients in the isoflurane group gave an opinion on odour. Ten minutes after operation, if the patient could sit up comfortably, the tapping test was performed and, if the result exceeded 90% of the preoperative value, the patient tried to stand. If these tests were satisfactory, a finger–nose test with eyes closed was performed before an attempt at a 10-m walk in a straight line, a turn and return. Tests were repeated at 5-min intervals until the walking test had been completed successfully; recovery times were calculated to this point.

An assessment of anxiety was made using a visual analogue scale before discharge and note made of the patient's memory for leaving the dental chair, the dental procedure and injections of local analgesic. Recalled injections were graded as acceptable, unpleasant or painful. Finally the patient gave a general opinion of the procedure.

Side effects over two days after operation were assessed by means of a separate form based on that described by Smith and Young [11].

RESULTS

Eighty patients participated in the trial: nine men and 31 women in the midazolam group and eight men and 32 women in the isoflurane group. Forty-four patients had surgical removal of wisdom teeth; 14 of these required extraction of teeth in more than one quadrant. Eighteen patients had multiple extractions and 14 others required apicectomies, two curettage, one excision of a cyst and another, closure of an oroantral fistula. The range of operations was similar in the two groups.

The mean dose of midazolam was 5.2 mg

TABLE I. *Demographic data and operative details (mean (SD)). VAS = Visual analogue scale; LA = local analgesia.* ***P < 0.001 *(Mann–Whitney* U *test)*

	Midazolam group	Isoflurane group
No. patients	40	40
Age (yr)	28.5 (9.4)	27.5 (7.4)
Weight (kg)	64.8 (12.1)	61.8 (11.7)
Corah dental anxiety scale	10.9 (3.6)	11.4 (3.7)
Anxiety VAS (cm)		
Before operation	6.5 (2.6)	6.5 (2.1)
After operation	1.3 (1.4)	1.2 (1.4)
Duration of operation (min)	28.7 (10.9)	31.5 (14.5)
Time to injection of LA (min)	6.3 (1.6)	7.7 (2.3)***
Recovery time (min)	16.1 (5.3)	12.2 (3.6)***
Arterial pressure (mm Hg)		
Before operation		
Systolic	130 (21.2)	122 (12)
Diastolic	79 (10.1)	78 (10.5)
After operation		
Systolic	123 (15.6)	127 (12.3)
Diastolic	76 (11.1)	78 (8.7)

(range 3–9 mg). The dose of midazolam was unrelated to the weight of the patient (Pearson $r = 0.147$). In the second group the concentrations delivered by the vaporizer, after initial induction, ranged from 0.4% to 1.2%. The mean concentration at 20 min (or 15 min for three patients in whom the operation finished before 20 min) was 0.72%.

Verbal contact was maintained in all patients given midazolam. One patient in the isoflurane group became excessively drowsy 15 min after induction, at a vaporizer concentration of 0.8%. Conscious sedation returned within 30 s of ceasing administration of isoflurane and sedation was maintained with 0.4–0.6% isoflurane.

The groups were comparable for age, weight and preoperative anxiety (table I). Seven patients had a Corah score greater than 17, a degree approaching phobia, and these patients needed reassurance to sit in the dental chair. There was a significant correlation ($r = 0.476$, $P < 0.01$) between the Corah and preoperative visual analogue scores. The visual analogue anxiety scores decreased after operation to similar values in each group (table I).

The durations of surgery were similar, but the time for induction of sedation was significantly longer in the isoflurane group ($P < 0.001$). The recovery time to completion of the walking test was significantly longer in the midazolam group ($P < 0.001$).

Pre- and postoperative arterial pressure and heart rates were comparable, but during the operation mean heart rate at 15 min in the midazolam group (97.1 beat min^{-1}) was greater than the preoperative mean (86.0 beat min^{-1}) and greater than the mean at 15 min in the isoflurane group (88.8 beat min^{-1}) ($P < 0.001$ in each case; Mann–Whitney U test). No arrhythmias were observed and heart rate always exceeded 58 beat min^{-1}.

Mean Sa_{O_2} in patients breathing isoflurane in oxygen was significantly greater than that in the midazolam group ($P < 0.001$; Mann–Whitney U test). Sa_{O_2} always exceeded 90% in the midazolam patients, but nine of these patients had intermittent Sa_{O_2} values of 90–94%. All but one were heavier than the group average (mean weight 77.6 (12.5) kg; group mean weight 64.8 (12.1) kg).

In the opinion of the dental surgeon, five patients gave an exaggerated response to injection of local analgesic in the isoflurane group, but none did so in the midazolam group (table II). With one very anxious patient (Corah score of 16) in the isoflurane group, conditions were judged inadequate. The dental surgeon judged the patients as more frequently calm and oriented after midazolam and more frequently euphoric after isoflurane.

In both groups the patients' mean estimate of the duration of the operation was approximately 50% of the true value (table III). Amnesia for injection of local analgesic was more likely after midazolam. Fifteen patients in the isoflurane group reported that the injections of local analgesic were unpleasant or painful, compared with six in the midazolam group ($P < 0.05$). Both techniques were rated as satisfactory in the patients' general opinion and only one patient of each group said that she would not wish to have the technique again; with midazolam, the patient said she had felt "unpleasantly weird", while with isoflurane the patient said she disliked the smell. While accepting the technique, another three patients (one midazolam and two isoflurane) would have preferred general anaesthesia; one in the isoflurane group would have preferred an injection technique.

Postoperative questionnaires were returned by 31 patients in the midazolam group and 34 in the isoflurane group (table IV). There was a similar high frequency of side effects in both groups. To give an index of the overall incidence of side

TABLE II. *Surgical assessment of sedation (No. of patients).* *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ *(Chi-squared test with Yates' correction)*

	Midazolam group	Isoflurane group
Total number of patients	40	40
Patients' response to injection		
None	16	16
Slight	24	19
Exaggerated	0	5
Operative conditions		
Satisfactory	37	35
Adequate	3	4
Inadequate	0	1
Patients' condition		
Calm and oriented	37	29*
Euphoric	1	11**
Drowsy	36	32
Prop used	2	2
Ptosis		
None	3	30
Slight	32	8
	> 37	> 10***
Marked	5	2

TABLE III. Patients' asessment of sedation (No. of patients). *$P < 0.05$; ***$P < 0.001$ (Chi-squared test, with Yates' correction). LA = Local analgesia. †One patient recalled the injections as both acceptable and unpleasant

	Midazolam group	Isoflurane group
No. patients	40	40
Estimation of mean (SD) duration of the procedure (min)	14.4 (9.7)	17.4 (14.1)
Remembered		
Leaving chair	38	40
Dental extractions (or procedure)	28	30
Injections of LA	25	39***
Opinion of LA (if remembered)		
Acceptable	19	25†
Unpleasant	5	11†
	> 6	> 15*
Painful	1	4
Opinion of odour inhaled		
Unpleasant	—	3
Slightly unpleasant	—	5
Pleasant	—	12
No smell or no opinion	—	20
General opinion		
Comfortable and relaxed	34	29
Comfortable but anxious	3	7
Anxious	2	2
Would have same sedation again	39	39

TABLE IV. Postoperative side effects (No. of patients)

	Midazolam group ($n = 31$)		Isoflurane group ($n = 34$)	
	Day 1	Day 2	Day 1	Day 2
Drowsiness	18	8	22	11
Lack of ability to concentrate	10	5	11	6
Dizziness or unsteadiness	9	6	9	3
Vomiting	0	1	0	0
Sick feeling without vomiting	4	5	9	3
Headache	8	7	11	6
Muscle ache or stiffness	7	5	9	11
Pain at the place of the dental procedure	24	21	27	15
Pain at the site of the injection in the hand	3	1	—	—
Sore throat	5	4	9	8
Time of return to usual work or housework				
Same day	2		3	
Next day	10		14	
Later	17		14	
Total side effects score (patient-days) (SD)	4.7 (3.5)		5.2 (3.3)	

effects, a score of 1 was given for each day a side effect was reported. The mean scores were similar in the two treatment groups.

The overall results were analysed to determine any significant trends between anxiety and other factors. There was no significant relationship between the concentration of isoflurane used and the patient's anxiety, but the dose of midazolam was greater in patients with more anxiety as assessed on the preoperative visual analogue scale ($r = 0.454$, $P < 0.01$). The total side effects score was related to postoperative anxiety (VAS) (rank correlation: $r = 0.304$, $P < 0.05$).

DISCUSSION

Lindsay and his colleagues reported that 31% of adults would prefer to receive sedation or anaesthesia for dental treatment [12]. We found that both midazolam and isoflurane gave satisfactory sedation, but identified some differences.

Midazolam has the advantage of a wide therapeutic ratio between sedative and anaesthetic doses. Conscious sedation, as defined by the maintenance of verbal contact [13] was achieved readily. As midazolam produces a peak effect early after injection, patients are generally well sedated at the time of the injection of local analgesic and less likely to report injections as unpleasant. We found that the dose of midazolam required was related to anxiety rather than weight of the patient, and we would not recommend the use of any weight-related dose in case this leads to a relative overdose and hypoxia.

Isoflurane has a small therapeutic ratio, so care is required to achieve conscious sedation. Because of this, and the odour of isoflurane, induction of sedation is slower and the degree of sedation and amnesia at the time of injection of local analgesic may not be optimal. A high degree of air dilution is inevitable during dental sedation [14] and this adds to the difficulty in selecting an appropriate vaporizer concentration. However, the degree of sedation can be reduced rapidly and this flexibility is lacking with midazolam. Another advantage of isoflurane is that recovery is more rapid than with midazolam and this may be important, as some patients ignore advice and return to work or drive cars shortly after treatment [15].

It would appear reasonable to restrict isoflurane sedation to circumstances when a second qualified person is present in addition to the operator. Isoflurane sedation may be considered for dental work in patients who are known to react adversely or have developed tolerance to benzodiazepines [16], or in patients who have an excessive fear of i.v. injections. Sedation with isoflurane is contraindicated in patient with a mask phobia and is less convenient for operations on anterior maxillary teeth when the Dupaco mask can be a hindrance to the surgeon. For other occasions, the choice between isoflurane and midazolam depends on the relative merits of more rapid induction with midazolam and more rapid recovery with isoflurane.

ACKNOWLEDGEMENTS

We are grateful to Roche Products Limited for financial support and to Penlon Limited for the prototype isoflurane vaporizer.

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CARDIOVASCULAR EFFECTS OF PROPOFOL IN THE ANAESTHETIZED DOG

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SUMMARY

This study was designed to investigate if propofol produced cardiovascular effects by direct actions or by indirect actions secondary to depression of the central nervous system. Experiments were performed on chloralose anaesthetized dogs in which all neurogenic cardiovascular reflexes were abolished by bilateral vagotomy and common carotid ligatures, in combination with i.v. bretylium and propranolol. Bolus doses of propofol followed by infusions at rates up to 160 mg kg^{-1} h^{-1} produced blood concentrations of propofol from 1.99 to 112 μg ml^{-1}. Infusions of hydroxyethyl starch given to maintain central venous pressures and pulmonary artery occlusion pressures at control values were used as an index of changes in capacitance. Blood concentrations of propofol less than 10 μg ml^{-1} caused an increase in mean capacitance of 8.0 (SEM 1) ml kg^{-1} with no significant changes in systemic vascular resistance, pulmonary vascular resistance or inotropic state of the heart. We conclude that anaesthesia with propofol may be accompanied by decreased cardiac output secondary to reduction in preload by a direct venodilator effect. Our experiments indicate that cardiac output and arterial pressure are preserved well at normal anaesthetic blood concentrations of propofol if the preload is maintained.

Induction of anaesthesia with propofol is accompanied by a decrease in arterial pressure in association with decreases in cardiac output and systemic vascular resistance [1–4]. Many of these changes occur secondary to altered sympathetic nervous system activity caused by loss of consciousness. Other human studies concluded that cardiovascular depression caused by propofol was greater than that with other anaesthetics, including thiopentone [5–9], methohexitone [6] and alphaxalone–alphadolone [10]. These differences may be the result of different depths of anaesthesia, although some studies [7,8] used equipotent doses of agents. It is still possible, however, that the differences between agents may be secondary to differences in central nervous system effects. The alternative explanation for the greater cardiovascular depressant effect of propofol is that it may have some direct influence on the cardiovascular system.

This study was designed to determine if propofol has a direct effect on systemic or pulmonary vasculature or on the heart. An anaesthetized dog preparation was chosen in which all neurogenic cardiovascular reflexes had been abolished [11]; thus influences produced by deepening planes of anaesthesia on the cardiovascular system by changing sympathetic or vagal tone were abolished.

MATERIALS AND METHODS

Anaesthesia was induced in five adult beagles (weight 10.5–16 kg) with an i.v. bolus injection of alpha chloralose 100 mg kg^{-1} and maintained with a dose of 10 mg kg^{-1} i.v. every 20 min throughout the experiment. Previous studies have shown that this produces a steady state light plane of anaesthesia with a stable baseline in cardiovascular variables [11]. Tracheotomy was performed and the lungs ventilated with a mixture of oxygen and air ($F_{I_{O_2}} = 0.4$) and a tidal volume of 10 ml kg^{-1}; the ventilator rate was adjusted to maintain normocapnia. Two catheters (2 mm i.d., Portex) were inserted into the descending aorta, one by each femoral artery; one was used for sampling blood for measurements of blood-gas, acid–base

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status, haematocrit and blood concentration of propofol, and the other for measurement of arterial pressure (AP) using a Statham P23 ID transducer. A Portex catheter (2 mm i.d.) was passed into the inferior vena cava from each femoral vein for the administration of fluids and measurement of central venous pressure (CVP) using a Gould disposable transducer. Needle electrodes were inserted into both forelegs and into the abdomen for monitoring ECG. Oesophageal temperature was monitored and kept within physiological limits by circulation of warm water through the surface of the operating table.

Bilateral cervical vagotomy was performed and both common carotid arteries were ligated. A pulmonary artery thermodilution catheter (7-French gauge, Edwards Laboratories) was inserted into the pulmonary artery via the right external jugular vein; this was used for measuring pulmonary artery pressure (PAP) and pulmonary artery occlusion pressure (PAOP) using a Gould disposable transducer. Cardiac output (Qt) was measured by the thermodilution method using Ringer's solution 3 ml at 0 °C injected into the right atrium. Left ventricular pressure measurements were made using a Portex catheter (10 cm long, 2 mm i.d.) introduced through the aortic valve via the left carotid artery. This catheter was attached to a Gould P23 ID transducer and pressure processor amplifier with differentiator (frequency response of whole system 0–50 Hz); the maximum differentiated signal (dp/dt_{max}) was used as an index of the inotropic state of the heart. The ECG leads and other pressure transducers were connected to Gould 4700 amplifiers and the resultant waveforms displayed on a Gould ES 1000 electrostatic recorder and video monitor.

LV and AP transducers were calibrated (0–300 mm Hg) with a mercury manometer and a water-filled manometer was used to calibrate CVP and PAP readings 0–50 mm Hg to an accuracy of 0.1 mm Hg before the start and after the end of the experiment. The differentiator of the pressure processor was calibrated using a sine-wave generator. The amplitude of the sine wave was adjusted to be equivalent to 200 mm Hg and the angular velocity calculated by the formula $2\pi af$ where a = amplitude of the sine wave and f the frequency of oscillation. A calibration curve of $2\pi af\ v.dp/dt_{max}$ obtained from the differentiation was plotted for a number of frequencies (0.5–10 Hz) at the end of each experiment. The traces on the chart recorder were corrected for catheter tip zero position at the end of the experiment after the animal was killed.

After surgical preparation, bretylium tosylate 5 mg kg^{-1} i.v. and propranolol 0.5 mg kg^{-1} i.v. were administered first as boluses and subsequently repeated by slow infusions over the next 1 h. A bipolar pacing wire attached to a stimulator (Digitimer DS2) was advanced from the left external jugular vein into the right atrium. The heart was overpaced using atrial pacing at a constant rate of 2.5 Hz (3–6 V, 2 ms pulse width) throughout the study. After checking the depth of anaesthesia, the animal was paralysed with suxamethonium 1 mg kg^{-1} i.v. bolus, followed by 3 mg kg^{-1} h^{-1} infusion. A period of 30 min was allowed for all cardiovascular variables to stabilize.

The following doses of propofol were administered i.v. in succession: (a) 10 mg kg^{-1} bolus followed by 20 mg kg^{-1} h^{-1} infusion for 30 min; (b) 10 mg kg^{-1} bolus followed by 40 mg kg^{-1} h^{-1} infusion for 30 min; (c) 10 mg kg^{-1} bolus followed by 80 mg kg^{-1} h^{-1} infusion for 30 min; (d) 10 mg kg^{-1} bolus followed by 160 mg kg^{-1} h^{-1} infusion for 30 min.

During the 30 min infusion period, hydroxyethyl starch (HES) was administered i.v. if the CVP or PAOP decreased to less than control values; the volume of HES administered was noted at the end of each stage (a, b, c and d). Measurements of Qt (mean of three readings), AP, CVP, PAP, PAOP, dp/dt_{max} were made during a control period before the administration of propofol and then at the end of each 30-min infusion period. At the end of each infusion period, arterial blood was withdrawn for measurements of blood-gas tensions, acid–base status, haematocrit and blood concentration of propofol. Recordings were made of the oesophageal temperature at the same time. Blood concentrations of propofol were measured by high pressure liquid chromatography by Dr E. J. Douglas, ICI Pharmaceuticals Division. Analysis of variance (ANOVAR) was used to test for statistical differences between the means of the test data and control readings. $P < 0.05$ was considered statistically significant. The study was performed under Home Office Project Licence No. PPL 50/00130.

RESULTS

Mean (SEM) values of Pa_{O_2} and Pa_{CO_2} (20.2 (0.4) kPa, 5.2 (0.0) kPa, respectively), arterial pH (7.37(0.06)) and body temperature (40.0 (0.1) °C)

TABLE I. *Blood concentrations of propofol measured after each stage of the propofol regimen, when a 10-mg kg^{-1} i.v. bolus in each case, was followed by a 30-min infusion of 20 mg kg^{-1} h^{-1} for 30 min (stage a); 40 mg kg^{-1} h^{-1} (stage b); 80 mg kg^{-1} h^{-1} (stage c); or 160 mg kg^{-1} h^{-1} (stage d)*

	Blood concentration of propofol (μg ml^{-1})			
	Stage a	Stage b	Stage c	Stage d
Mean (SEM)	3.44(0.46)	9.07(1.15)	21.78(2.78)	75.74(13.07)
Range	1.99–4.80	6.23–13.10	14.30–30.00	36.20–112.00

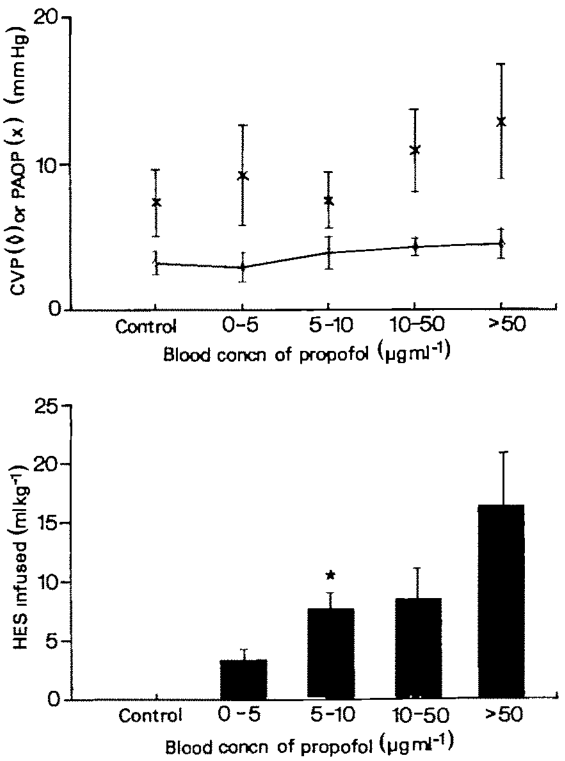

FIG. 1. Capacitance and preload (mean (SEM)) at different blood concentrations of propofol. The CVP and PAOP were kept at values which were not statistically different from control by infusions of hydroxyethyl starch (HES), cumulated volumes of which are shown in the bottom panel. The major capacitance changes occurred at blood concentrations of propofol < 10 μg ml^{-1}. Infusions of HES of 3 (1) ml kg^{-1} were necessary to keep CVP and PAOP at control values for blood propofol concentrations 0–5 μg ml^{-1}. Further significant (*$P < 0.05$) volumes of HES were necessary, to a total of 8 (1) ml kg^{-1}, at blood concentrations of propofol 5–10 μg ml^{-1}.

were maintained within physiological limits. The doses of propofol given produced blood concentrations which were consistent between animals (table I); the lower infusion rates of 20 mg kg^{-1} h^{-1} (a) and 40 mg kg^{-1} h^{-1} (b) produced blood concentrations of drug from 1.99 to 13.1 μg ml^{-1} (the anaesthetic range in man) [11]. Infusion regimens (c) and (d) produced blood concentrations of propofol in the range 14.3–112.0 μg ml^{-1}.

Cardiovascular variables have been grouped according to blood propofol concentration: control values ($n = 5$); values at concentrations 0–5 μg ml^{-1} ($n = 5$); 5–10 μg ml^{-1} ($n = 4$); 10–50 μg ml^{-1} ($n = 6$); and greater than 50 μg ml^{-1} ($n = 5$). CVP and PAOP did not change significantly from the control readings as the concentration increased. It was necessary to infuse HES 8 (SEM 1) ml kg^{-1} in order to maintain constant CVP and PAOP at concentrations of propofol up to 10 μg ml^{-1}. Further infusions of HES were necessary to keep the CVP and PAOP at control values with blood propofol concentrations greater than 50 μg ml^{-1}, but these were not significantly different from the values for 10–50 μg ml^{-1} (fig. 1).

Qt increased slightly but not significantly over the range of blood propofol concentrations (fig. 2). At blood concentrations of propofol less than 10 μg ml^{-1}, dp/dt_{max} was unchanged and there were slight but insignificant decreases in SVR and PVR. At values greater than 10 μg ml^{-1} there was a progressive decrease in SVR and PVR, accompanied by decreases in haematocrit and dp/dt_{max}. The changes in PVR were not significant. Values of dp/dt_{max} and SVR were significantly reduced compared with control at blood concentrations of propofol > 50 μg ml^{-1} and 10 μg ml^{-1}, respectively.

Regression analysis was performed to compare the cardiovascular measurements with each other and the blood propofol values. There was no significant correlation between the whole range of blood concentrations of propofol and *Qt*, PVR or SVR, and no correlation between the whole range of *Qt*, haematocrit, and PVR or SVR.

DISCUSSION

In this study, blood concentrations of propofol which are considered to be subanaesthetic and

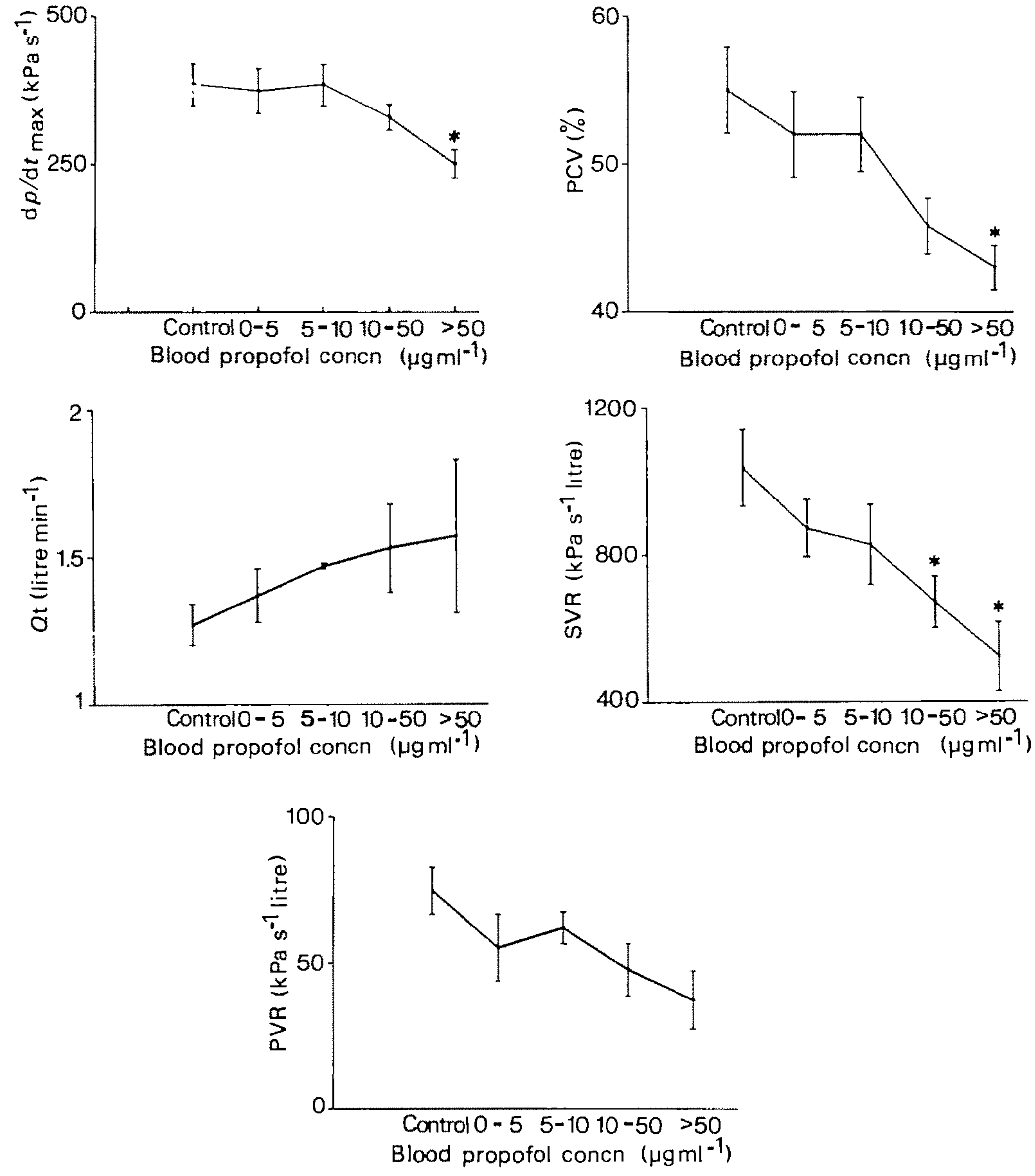

FIG. 2. Direct effects of propofol on the heart and systemic and pulmonary vascular beds (mean (SEM)). No significant changes in *Qt* or pulmonary vascular resistance (PVR) occurred. Statistically significant (*$P < 0.05$) decreases in systemic vascular resistance (SVR) and dp/dt_{max} occurred at blood concentrations of propofol > 10 µg ml^{-1}. PCV = Packed cell volume (haematocrit).

anaesthetic in man (i.e. < 10 µg ml^{-1} [12]) caused dose-dependent increases in capacitance by a direct venodilator effect. No significant changes in SVR, *Qt*, PVR or dp/dt_{max} occurred which might indicate a direct action of the drug on arteriolar smooth muscle or on the myocardium. At greater blood concentrations of propofol (> 10 µg ml^{-1}) there was a direct arteriolar vasodilator effect which caused a significant decrease in systemic vascular resistance. Although there was no correlation between haematocrit values and SVR, some of the decrease in SVR was probably a result of decreased blood viscosity caused by the lower haematocrit at higher blood concentrations. The decrease in dp/dt_{max} at these higher values may reflect a negative inotropic effect of the drug, but part of this decrease may be explained by the decreases in systemic vascular resistance, because measurements of dp/dt_{max} depend also on variations of afterload. The capacitance changes at very much greater concentrations of propofol probably indicate a capacitance increase secondary to the arteriolar vasodilatation which occurs at these concentrations—that is, passive filling of peripheral veins and venules by increased blood flowing through peripheral tissues resulting from the arteriolar vasodilatation.

In pilot experiments, measurements of concentrations of propofol 5 min after 10–40 mg kg^{-1} i.v. boluses were low. This did not allow time for adequate cardiovascular stabilization and measurements on a steady baseline. The increasing dose regimen of four stages, each consisting of a bolus followed by an infusion for 30 min, aimed to achieve a steady baseline of cardiovascular variables and blood propofol concentration. Only single values of propofol were measured each 30 min in this study, so we do not know if the concentrations were changing. However, cardiovascular variables remained stable, allowing all the measurements, including blood-gas tensions and blood sampling, to be made within a 1-min period during which time no discernible changes occurred. We are able therefore, to compare cardiovascular measurements directly with the blood concentration of propofol. The variation in concentration between animals receiving the same dose was probably a result of differences in haemodilution by hydroxyethyl starch and, possibly, pharmacokinetic differences.

The animal preparation used in this study allows us to investigate the direct effects of an anaesthetic agent on the cardiovascular system in the intact animal in the absence of changes secondary to deepening anaesthesia; the changes mimic those in previous studies in which abolition of reflexes mediated by sympathetic nerves were totally abolished [11]. In addition, we cut both vagi and tied both common carotid arteries to eliminate possible reflex effects mediated via the vagus nerves. This does not lead to cerebral hypoxia because the dog receives a large part of its cerebral blood flow via the vertebral vessels. In any case, the cardiovascular system was devoid of nervous system control in this preparation. Thus the cardiovascular changes observed were the result of direct effects of propofol on the cardiovascular system, because all autonomic nervous system control of venomotor and arteriolar tone and inotropism had been abolished by surgical and pharmacological means.

It may be argued that measurement of capacitance changes by recording the volume of HES infused is inaccurate. Although the venous system is very distensible, we measured CVP and PAOP to the nearest 0.1 mm Hg with accurately calibrated transducers. The decreases in filling pressures following propofol were always 10–30 times the minimum value detectable and therefore we are confident that the capacitance changes measured were significant.

These data explain the findings of previous human studies which suggested that propofol decreases arterial pressure and cardiac output to a greater extent than thiopentone [7–9]. If one is to assume that equivalent doses of the two anaesthetic agents were given [13], one must conclude that, under those conditions, the changes in sympathetic nervous system outflow caused by induction of anaesthesia were the same for both drugs. However, in addition to the decrease in sympathetic tone caused by induction of anaesthesia or deepening anaesthesia at increased infusion rates [14], our study suggests that propofol also caused a decrease in preload. Further decreases in cardiac output and arterial pressure occur as a result of the decrease in preload, in addition to those caused by decreased sympathetic nervous system tone. Some human studies have noted decreases in CVP or PAOP during propofol anaesthesia [3,7,8,14,15]. These decreases in preload were probably caused by a combination of lower sympathetic tone in addition to the venodilatation caused by direct drug effect.

ACKNOWLEDGEMENTS

The authors thank Mr D. Myers for technical help and Dr E. J. Douglas and ICI for measurement of blood propofol concentrations.

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PREVENTION OF TOURNIQUET PAIN BY SPINAL ISOBARIC BUPIVACAINE WITH CLONIDINE

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SUMMARY

In order to assess the effect of spinal clonidine on tourniquet pain, 30 patients scheduled to undergo orthopaedic surgery under spinal anaesthesia were allocated randomly to two groups. Patients in group I ($n = 15$) *received 0.5% isobaric bupivacaine 15 mg plus isotonic saline 1 ml. Patients in group II* ($n = 15$) *received 0.5% bupivacaine 15 mg plus clonidine 1 ml (150 µg). Sensory block was evaluated by pinprick and motor block with Bromage's scale. The presence of clonidine significantly prolonged the duration of sensory and motor block. Three patients in group I, but none in group II, experienced tourniquet pain. Hypotension and bradycardia were not worsened by spinal clonidine. The use of clonidine may be a useful technique to augment bupivacaine spinal block.*

Tourniquet pain (TP) occurs under regional anaesthesia in patients undergoing orthopaedic surgery. It is described as a tight or burning sensation unrelated to the surgical field [1,2]. Several attempts have been made to decrease the incidence of TP during spinal anaesthesia; for example, TP was less frequent when bupivacaine was administered instead of amethocaine and when an isobaric instead of a hyperbaric, solution was used [3–7]. Nevertheless, TP has been observed even when isobaric bupivacaine solution has been used for spinal anaesthesia [5–7]. Clonidine, an alpha-2 agonist agent, has been shown in animal studies to increase the duration of sensory and motor block produced by local anaesthetic agents administered into the subarachnoid space [8,9]. Prolongation of isobaric bupivacaine spinal anaesthesia by clonidine has also been described in man, without significant side effects [10]. We have observed elsewhere as a coincidental finding that TP was decreased by the addition of clonidine to spinal amethocaine [11]. We have therefore conducted a formal randomized prospective study in order to see if the addition of clonidine attenuates TP during spinal anaesthesia.

MATERIAL AND METHODS

We studied 30 patients after obtaining institutional Ethics Committee approval and informed consent from each individual.

Patients were allocated randomly to two groups: group I ($n = 15$) received 0.5% isobaric bupivacaine 15 mg with isotonic saline 1 ml injected into the subarachnoid space; group II ($n = 15$) received 0.5% isobaric bupivacaine 15 mg plus clonidine 1 ml (150 µg). The anaesthetic procedure was standardized: with the patient in the sitting position, spinal anaesthesia was performed at L3–4 using a 25-gauge needle. Patients were then turned to the supine position and the level of sensory block evaluated by pinprick and motor block graded from 0 to 3 on Bromage's scale. Evaluation of block was performed by an independent observer at 5, 10, 15 and 20 min after the spinal injection and then at 10-min intervals until the complete resolution of the sensory and motor block.

The ECG (CM5 configuration) was monitored continuously and arterial pressure and heart rate were measured every 3 min for 20 min and every 5 min subsequently using an automated oscil-

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lometric device (Dinamap, Critikon). A pneumatic tourniquet was placed at the origin of the corresponding lower limb which had been exsanguinated with an Esmarch bandage. The tourniquet was inflated to 400 mm Hg and left in place during surgery. When patients complained of pain during surgery it was considered to be induced by the tourniquet if it was unrelated to the surgical field, described as an uncomfortable sensation in the corresponding lower limb, not localized precisely, and which disappeared with release of the tourniquet.

Data were analysed using two-way analysis of variance, paired and unpaired Student's *t* test and the Fisher exact test. Values are expressed as mean (SD) and a value of $P < 0.05$ was taken as significant.

RESULTS

Patients were comparable in the two groups for mean age, weight, height and sex, and for mean durations of tourniquet inflation (table I). In the clonidine–bupivacaine group, the durations of sensory and motor block were prolonged significantly compared with group I, while the extent of sensory block was similar in the two groups (table II). Three patients in the bupivacaine plain solution group experienced typical TP (table III), but no patient in the bupivacaine–clonidine group complained of pain ($P = 0.1$). Significant

TABLE I. *Clinical features of the patients (mean (SD))*

	Sex (F/M)	Age (yr)	Weight (kg)	Height (cm)	Duration of tourniquet inflation (min)
Group I: bupivacaine	6/9	39.4 (19.0)	70.1 (13.2)	171 (6)	80.5 (29.6)
Group II: bupivacaine + clonidine	4/11	40.4 (15.0)	72.3 (13.5)	172 (7)	85.0 (35.0)

TABLE II. *Features of spinal anaesthesia (mean (SD)). ** Significant difference (P < 0.01) between the two groups*

	Sensory block		Duration of motor block (min)		
	Maximum extent (segments)	Time for regression at L2 (min)	Grade 1	Grade 2	Grade 3
Group I: bupivacaine	12.5 (0.9) (T10–T11)	150 (19)	218 (20)	180 (25)	128 (26)
		**	**	**	**
Group II: bupivacaine + clonidine	13.4 (0.8) (T9–T10)	175 (16)	261 (12)	220 (25)	182 (26)

TABLE III. *Features of the three patients having tourniquet pain (TP). SB = Sensory block*

			At onset of TP		
Patient	Sex	Age (yr)	Duration of tourniquet inflation (min)	Extent of SB (segments)	Maximum extent SB (segments)
1	F	30	50	T 11	T 11
2	M	72	65	T 10	T 10
3	F	37	100	T 12	T 10

TABLE IV. *Haemodynamic changes during spinal anaesthesia (mean (SD)). c = Control values before spinal anaesthesia; min = minimum values during spinal anaesthesia. ** Statistical difference* ($P < 0.01$) *between control and minimum values within group*

	SAPc (mm Hg)		SAPmin (mm Hg)	DAPc (mm Hg)		DAPmin (mm Hg)	HRc (beat min^{-1})		HRmin (beat min^{-1})
Group I: bupivacaine	135 (12)	**	118 (19)	77 (12)	**	70 (10)	80 (17)	**	65 (11)
Group II: bupivacaine + clonidine	137 (20)	**	118 (10)	77 (16)	**	67 (11)	80 (9)	**	63 (7)

decreases in arterial pressure and heart rate occurred in both groups, but there was no significant difference between groups (table IV). One patient in each group had bradycardia (< 50 beat min^{-1}).

DISCUSSION

In this study, TP occurred in three of the 15 patients receiving spinal plain solution of bupivacaine. In a previous study the incidence of TP was 13.3% with 0.5% isobaric bupivacaine [5]. In these three patients, TP occurred within 1 h of tourniquet inflation in one patient and between 1 h and 2 h in the other two. It was associated with an upper level of sensory block equal to or above T12. TP does not seem to be related directly to the regression of sensory block [4–7, 12] and is thought to be mediated by stimulation of unmyelinated C-fibres [2]. Experimental data suggest that, under conditions of continuous stimulation, C-fibres are resistant to local anaesthetic-induced block [13]. The lack of precise segmental localization of TP, noted also in this study, also suggests an origin of TP from C-fibre stimulation.

Different techniques have been reported to prevent TP. The addition of morphine to spinal hyperbaric bupivacaine provides efficient prophylaxis [14]. The extradural injection of a combination of fentanyl and bupivacaine also prevents TP [15]. However, spinal or extradural opioids are associated with side effects such as respiratory depression or urinary retention [14, 16].

Clonidine produces antinociception in animals and humans, via an opioid-independent mechanism when administered intrathecally or extradurally [17–19]. Clonidine, which is mainly an alpha-2 adrenergic agonist, may stimulate alpha-2 receptors located in the dorsal horn of the spinal cord [20], resulting in inhibition of C-fibre evoked activity in dorsal horn neurones [21, 22]. There is an alternative mechanism. This study confirms that clonidine prolongs the duration of both sensory and motor block during spinal anaesthesia, as documented previously in humans [9, 10, 23]; clonidine has no direct motor blocking properties after spinal administration and it has been suggested that it decreases vascular absorption of bupivacaine. In several studies clonidine has been shown to decrease spinal blood flow [24, 25] and this may account for its action in prolonging and augmenting local anaesthetic-induced spinal block.

No significant side effects were observed in patients receiving spinal clonidine. The degree of hypotension and the incidence of bradycardia was similar in both groups. The haemodynamic effects of clonidine (usually hypotension and bradycardia) result from actions on brainstem and spinal cord to decrease sympathetic outflow [25]. In a previous study no significant haemodynamic effects were noticed when clonidine was combined with isobaric bupivacaine during spinal anaesthesia [9]. It is likely that the action of clonidine is masked by the sympathetic block produced by local anaesthetics.

We conclude that the addition of clonidine to isobaric bupivacaine for spinal anaesthesia prolongs sensory block and enhances its quality without important side effects. The results of this study in a limited number of patients suggest that spinal clonidine prevents tourniquet pain when associated with bupivacaine, although this requires confirmation in a much larger study.

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Br. J. Anaesth. (1989), **63**, 97–102

VENTILATORY RESPONSE TO CARBON DIOXIDE DURING EXTRADURAL ANAESTHESIA WITH LIGNOCAINE AND FENTANYL

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SUMMARY

Twenty-seven patients undergoing extracorporeal shock-wave lithotripsy or knee arthroscopy received extradural anaesthesia with 2% lignocaine plus adrenaline 1 in 200000. They were allocated randomly to three groups, one receiving no fentanyl ($n = 6$*), the two others receiving fentanyl 50 µg either extradurally (*$n = 15$*) or i.v. (*$n = 6$*). Three tests of sensitivity to carbon dioxide (Read's method) were performed successively on each patient: before operation and at 1 and 2 h after the extradural injection. Whereas lignocaine and adrenaline alone had no significant effects on basal ventilation and the ventilatory response to carbon dioxide, extradural fentanyl caused a slight reduction in resting ventilatory rate and ventilation at 1 and 2 h with no change in resting end-tidal carbon dioxide concentration. In addition, the slope of the ventilatory response to carbon dioxide was reduced slightly at 1 h and ventilation at end-tidal* P_{CO_2} *of 7.3 kPa was reduced also at 1 and 2 h. Conversely, the same dose of fentanyl i.v. had lesser and shorter effects on ventilation at rest and during carbon dioxide rebreathing. Our results show that fentanyl 50 µg given extradurally caused slight ventilatory depression which is probably clinically unimportant.*

Postoperative analgesia may be achieved by the use of extradural opioids [1–6] which enhance both the intensity and duration of analgesia produced by extradural local anaesthetics [7–10]. The most serious adverse effect associated with extradural injection of opioids is ventilatory depression [2,11–21]. As with other side effects, this is dose dependent and more likely to occur with lipid-insoluble opioids [12]. Fentanyl is highly lipid-soluble, and has a rapid onset of action (5–10 min) [22], producing good analgesia with a dose as small as 50 µg extradurally [18,22–24]. The respiratory depressant action of extradural fentanyl has been investigated previously in higher doses, usually in postoperative analgesia [4,5,24] by measurement of ventilatory response to carbon dioxide [25,26].

This study was designed to see if extradural anaesthesia (extending to T4) with a mixture of 2% lignocaine (with adrenaline 1 in 200000) and fentanyl 50 µg causes respiratory depression and to compare this with that, if any, caused by extradural lignocaine alone or with fentanyl 50 µg i.v.

PATIENTS AND METHODS

We studied 27 patients (ASA status I–II) requiring extradural anaesthesia for extracorporeal shock-wave lithotripsy (ESWL) ($n = 18$) or knee arthroscopy ($n = 9$). These procedures were chosen because of their brief duration (less than 60 min) and because they do not affect the mechanical properties of the lungs or chest wall. There were 19 males and eight females, age range 24–59 yr, weights 49–103 kg and heights 155–193 cm. No patient had clinical or radiological signs of chest disease. All patients gave informed consent for the study, which was approved by the local Ethics Committee. The ventilatory response to carbon dioxide was assessed by Read's method [27] the day before the procedure and, after operation, 1 and 2 h after the extradural injection.

The first part of the study was carried out in

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nine subjects undergoing ESWL under extradural lignocaine–fentanyl combination. The decrease in sensitivity to carbon dioxide documented previously with higher doses of fentanyl [25,26] was found also with the dose of 50 µg.

In the second part of the study, 18 other patients were allocated randomly to three groups of six each:

Group X-0 received only extradural 2% lignocaine with adrenaline 1 in 200000, without i.v. sedation.

Group X-F_{iv} received the same dose of extradural lignocaine with adrenaline and an i.v. injection of fentanyl 50 µg administered when the extradural injection was completed.

The third group received extradurally a mixture of 2% lignocaine with adrenaline 1 in 200000 and fentanyl 50 µg.

Thus a total of 15 patients received the extradural mixture of lignocaine and fentanyl: nine in the first part and six in the second part of the study. After the absence of significant differences between these two subgroups at rest and on carbon dioxide rebreathing was verified, they were pooled together and are termed X-F_{ext}.

Three overweight patients were graded ASA II (two in group X-F_{ext}, the third in group X-0).

The three groups were comparable in age, weight and height (table I).

Extradural anaesthesia

Patients were not premedicated and they fasted overnight. Arterial pressure and heart rate were recorded with an automatic monitor (Dinamap) and ECG was displayed continuously. An i.v. infusion was started and Ringer Lactate solution 1 litre was infused during the first 20 min. The total volume of i.v. infusion for the 2 h was 1500–2000 ml.

With the patient in the lateral position, extradural puncture was performed at either the T12 space for ESWL or the L2 space for knee arthroscopy. After a test dose of 2% lignocaine 3 ml with adrenaline 1 in 200000, 9 ml (T12) or 17 ml (L2) of the same anaesthetic solution with or without fentanyl 50 µg was injected slowly through the Tuohy needle. The spread of sensory block was assessed by altered sensation to pinprick at the time of the first postoperative carbon dioxide rebreathing test (i.e. 1 h after extradural injection). Three patients developed hypotension at the onset of anaesthesia and were treated with ephedrine 3 mg i.v. No side effects (pruritus, nausea or vomiting, urinary retention) were noted in the patients receiving fentanyl.

TABLE I. *Physical characteristics of the subjects (mean (SD))*

	n	Age (yr)	Height (cm)	Weight (kg)
Group X-0	6	41 (9)	172 (13)	72 (18)
Group X-F_{iv}	6	41 (12)	168 (10)	70 (15)
Group X-F_{ext}	15	37 (9)	169 (7)	69 (10)

Carbon dioxide rebreathing test

The ventilatory response to carbon dioxide was measured by Read's method [27] with a bag-in-the-box system. A 7-litre rebreathing bag was enclosed in a rigid, air-tight box with a side port connected to a Fleisch type 3 pneumotachograph and a Godart 17 212 differential pressure transducer. Wearing a tight fitting nasal mask and with the mouth closed, the patients breathed either room air or from the bag via a wide-bore respiratory circuit including a low resistance inspiratory/expiratory valve and a large three-way stopcock (Rudolph M 2 100). Carbon dixoide concentration in the expired gas was measured continuously by drawing gas from the mask at a flow rate of 500 ml min^{-1} through a Beckman LB-2 capnograph. During carbon dioxide rebreathing, the sampled gas was returned to the rebreathing bag. A two-channel recorder Allco ED 242-B was used to record ventilation and expired carbon dioxide concentration at a paper speed of 1 mm s^{-1}.

Baseline values were obtained the day before the procedure. The subject had no tea or coffee for 3 h and was at rest and seated comfortably for 10 min before the test. Postoperative tests were performed at 1 and 2 h following extradural anaesthesia (H_1 and H_2 values, respectively) while subjects reclined in bed at a 45° head-up position in the recovery-room.

The bag was filled with 5 litre of 7% carbon dioxide in oxygen at the start of each test and the subject breathed room air for approximately 5 min, during which time ventilation and end-tidal $P\mathrm{CO_2}$ ($P\mathrm{E}'_{\mathrm{CO_2}}$) were monitored. When stable ventilatory frequency and $P\mathrm{E}'_{\mathrm{CO_2}}$ had been achieved, resting values were recorded for 1 min, which allowed determination of minute ventilation ($\dot{V}\mathrm{E}$), respiratory rate (RR) and $P\mathrm{E}'_{\mathrm{CO_2}}$. The stopcock was turned to the rebreathing bag and the subject asked to take three large breaths. Rebreathing then continued for 4.5 min.

$P\mathrm{E}'_{\mathrm{CO_2}}$ and $\dot{V}\mathrm{E}$ were determined at 30-s intervals.

$\dot{V}E$ was calculated as the product of the mean of tidal volume and frequency of the three ventilatory cycles bracketing the moment of PE'_{CO_2} readings. The line of best fit of $\dot{V}E$ as a function of PE'_{CO_2} was calculated using a linear least square regression (as a non-linear description offers no advantage [28]). In addition, the goodness of fit shown by correlation coefficients (r) ranging between 0.91 and 0.98 ($P < 0.01$) allowed the determination of the slope $\dot{V}E/PE'_{CO_2}$ and the inter- or extra-polated value of $\dot{V}E$ for $PE'_{CO_2} = 7.3$ kPa ($\dot{V}E$ 7.3) [27,29].

Statistical analysis

As distribution of data was log-normally skewed, logarithmic transformation was performed [30]. Statistical comparisons were made using two-way analysis of variance for repeated measures followed by paired-sampled t tests to compare values at H_1 and H_2 with baseline values when the analysis of variance had disclosed significant intra-group differences. The chosen level of statistical significance was $P < 0.05$.

RESULTS

The height of analgesia attained T4–T5 in 18 of 27 patients with a range from T3 to T8 and no difference between groups. The range of the baseline slope $\dot{V}E/PE'_{CO_2}$ was 0.08–0.8 litre min^{-1} kPa^{-1}; that is, the ventilatory response to carbon dioxide was within the limits of normal responses in young adults [31]. Maximal values of PE'_{CO_2} at the end of the three tests were close in each patient, but between patients the variations were large, ranging from 6.7 to 9.3 kPa. In general, the greater the PE'_{CO_2} at onset, the greater it was at the end of the test. All values are given as mean (SD) in table II.

There was no difference between the observed variables for the three groups at the time of baseline measurements.

In group X-0 at 2 h lignocaine with adrenaline caused an increase in $\dot{V}E$, a decrease in PE'_{CO_2} and an increase in ventilatory response to carbon dioxide. However, these variations were not significant. In contrast, in the two groups receiving fentanyl there was evidence of slight ventilatory depression. In group $X\text{-}F_{iv}$, resting ventilatory frequency was slower and resting $\dot{V}E$ lower at 1 h but it returned to normal at 2 h, and the ventilatory response to carbon dioxide was not changed. In group $X\text{-}F_{ext}$ at rest, ventilatory frequency was slower both at 1 and 2 h and $\dot{V}E$ was decreased with $\dot{V}E$ being lower at both time points than at baseline in 11 of 15 subjects. It is

TABLE II. *Ventilation at rest and ventilatory response to carbon dioxide rebreathing (mean (SD)).* PE'_{CO_2} *= end-tidal partial pressure of carbon dioxide; RR = respiratory rate;* $\dot{V}E$ *= expiratory minute ventilation;* $\dot{V}E/PE'_{CO_2}$ *and* $\dot{V}E$ *7.3 = slope of the line of best fit of* $\dot{V}E$ *as a function of* PE'_{CO_2} *and* $\dot{V}E$ *at* $PE'_{CO_2} =$ *7.3 kPa during carbon dioxide rebreathing. Group X-0 = lignocaine;* $X\text{-}F_{iv}$ *= lignocaine + i.v. fentanyl;* $X\text{-}F_{ext}$ *= lignocaine + extradural fentanyl. *Significant difference (P < 0.05) from baseline*

	Baseline	1 h	2 h
Resting PE'_{CO_2} (kPa)			
Group X-0	5.1 (0.68)	4.8 (0.72)	4.9 (0.62)
Group $X\text{-}F_{iv}$	4.73 (0.78)	4.7 (0.69)	4.8 (0.48)
Group $X\text{-}F_{ext}$	5.2 (1.0)	5.1 (0.73)	5.3 (0.53)
Resting RR (b.p.m.)			
Group X-0	13.2 (4.6)	11.8 (2.6)	13.6 (2.0)
Group $X\text{-}F_{iv}$	14.2 (3.7)	11.0 (2.8)*	12.9 (2.4)
Group $X\text{-}F_{ext}$	15.6 (4.4)	14.2 (3.9)*	13.4 (3.6)*
Resting $\dot{V}E$ (litre min^{-1})			
Group X-0	6.4 (0.8)	7.0 (1.3)	7.8 (3.6)
Group $X\text{-}F_{iv}$	7.6 (1.5)	6.1 (4.1)*	6.8 (1.7)
Group $X\text{-}F_{ext}$	8.1 (2.5)	5.9 (1.8)*	5.9 (1.4)*
Slope $\dot{V}E/PE'_{CO_2}$ (litre min^{-1} kPa^{-1})			
Group X-0	0.23 (0.08)	0.23 (0.09)	0.27 (0.11)
Group $X\text{-}F_{iv}$	0.21 (0.05)	0.21 (0.11)	0.25 (0.08)
Group $X\text{-}F_{ext}$	0.24 (0.17)	0.20 (0.21)*	0.21 (0.17)
$\dot{V}E$ 7.3 (litre min^{-1})			
Group X-0	20.2 (7.5)	26.1 (12.8)	24.8 (12.5)
Group $X\text{-}F_{iv}$	20.4 (6.0)	19.1 (10.3)	19.7 (9.0)
Group $X\text{-}F_{ext}$	19.9 (16.0)	18.8 (23.2)*	16.2 (12.7)*

noteworthy that the slope of the ventilatory response to carbon dioxide decreased by more than 20% from baseline in eight of 15 patients receiving extradural fentanyl and increased by more than 10% in only one. In addition, there was a decrease in ventilatory response to carbon dioxide in group X-F_{ext}. The slope $\dot{V}E/PE'_{CO_2}$ at 1 h but not at 2 h was less steep than at baseline, and $\dot{V}E$ 7.3 was reduced at 1 and 2 h. However, there was no significant increase in PE'_{CO_2} at rest.

DISCUSSION

Our results confirm that a low dose of fentanyl 50 μg injected extradurally (irrespective of the presence of lignocaine and adrenaline), caused slight ventilatory depression. The small decrease in frequency, minute ventilation and ventilatory response to carbon dioxide is consistent with the effects of other extradural opioids [2–4, 10, 19, 22].

We used only single estimates of the carbon dioxide response at each stage of our study, and this may be insensitive. Indeed, it has been shown by Goodman and Curnow that the coefficient of variation of the slope of the ventilatory response to carbon dioxide was about 20% with Read's method in four normal subjects studied on 3 days and 10 occasions over 1 month [28]. In our subjects there was a mean reduction of 16.6% from baseline at 1 h after extradural fentanyl (table II). There are four reasons why we believe that this change is real. First, it confirms established results: diamorphine depresses the carbon dioxide response slope after 30 min [13, 19]; a single extradural injection of fentanyl 200 μg depresses ventilation also at 30 min, maximally at 1 h and decreasing slowly at 2 and 3 h [25]; a priming dose of fentanyl 1 $\mu g\ kg^{-1}$ followed by a continuous extradural infusion of 1 $\mu g\ kg^{-1}$ depresses the carbon dioxide response slope at 1 h by 47.9% [26]. Second, the slope of the ventilatory response to carbon dioxide measured at 15-min intervals in 111 young normal subjects was highly reproducible [31]. Third, not only was the slope of the ventilatory response depressed, but $\dot{V}E$ 7.3 was reduced also with extradural fentanyl (table II). Fourth, because of the high correlation coefficient (≥ 0.91, $P < 0.01$) of the linear regression of $\dot{V}E$ as a function of PE'_{CO_2}, the 95% confidence interval was at most 20% of the group average slope [29].

However, the magnitude of the response was small and less than that occurring with higher doses of fentanyl [25, 26], and it is probably of little, if any clinical relevance.

The ventilatory depression produced by extradural opioids has been attributed to diffusion of the drug either within the CSF [32] or through the venous spinal blood flow towards cerebral vessels [2]. The blood concentration of fentanyl attained after extradural injection of 200 μg was too low to produce respiratory depression [4, 25]. Ventilatory depression probably lasts a little longer than the period used in this study, as elimination of fentanyl takes more than 2 h [33]. That fentanyl was responsible for the slower rate of ventilation is suggested by the lack of change in group X-0. However, a slower rate of ventilation was not found by Gaffud and colleagues with fentanyl 100 μg [9], by Negre and co-workers with 200 μg [25] or by Torda and Pybus with 60 μg [24].

It is unlikely that the lignocaine and adrenaline used in this study were responsible for the slight depression of ventilation. Adrenaline alone (50 μg in 10 ml of saline) was injected extradurally in a young volunteer by Bromage and colleagues, who reported that "objective signs of limited segmental (T10–L2) hypoalgesia developed 20 min after injection, and lasted about 6 hours", but the carbon dioxide response curve did not change from control [34]. Klepper and colleagues compared the effects of extradural sufentanil alone or with adrenaline and observed that the extent of respiratory depression was similar [35].

Extradural analgesia with lignocaine does not modify the ventilatory response to acute carbon dioxide challenge. In patients who had undergone prosthetic replacement of the lower aorta, no significant decrease in ventilatory response to carbon dioxide was found on the first day after operation [13], and others found no change with extradural chloroprocaine 500-800 mg [14]. In healthy patients, functional residual capacity and vital capacity do not change after extradural anaesthesia with sensory block to T3 [36].

Toxic effects of local anaesthetics on the central nervous system (CNS) are well documented and occur at blood concentration much higher than those likely to be present in our patients. "During the phase of CNS excitation prior to development of frank convulsions, an increased respiratory rate may be observed in patients. Animal studies in dogs and sheeps have shown that these animals tend to hyperventilate during convulsive activity such that little changes in pO_2 and pCO_2 is seen"

[37]. Our data accord with this hypothesis that hyperventilation preceeds convulsions, as slight, although not significant, variations in ventilation at rest and in response to carbon dioxide were observed, consistent with a stimulating effect of extradural lignocaine.

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Br. J. Anaesth. (1989), **63**, 103–108

ETHANOL-INDUCIBLE CYTOCHROME P450 IN RABBITS METABOLIZES ENFLURANE†

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SUMMARY

Following anaesthesia with enflurane, some patients receiving isoniazid have increased serum concentrations of fluoride ion, presumably because of induction of an isozyme of cytochrome P450 which is responsible for enflurane biodegradation. In rats, isoniazid and ethanol enhance metabolism of enflurane and also induce a form of cytochrome P450 which is homologous with a form of rabbit liver cytochrome P450 known as 3a. Isoniazid, ethanol and imidazole increase the concentration of cytochrome P450 3a in hepatic microsomes. We have pretreated rabbits with imidazole, the most potent of the three inducers of isozyme 3a, to determine if the hepatic microsomal metabolism of enflurane is enhanced and if purified isozyme 3a catalyses the oxidation of enflurane. Imidazole produced a 250% increase in the hepatic microsomal metabolism of enflurane, sevoflurane, methoxyflurane and the control substrate, aniline. Polyclonal antibodies to cytochrome P450 3a inhibited 90% of enflurane metabolism, but only 40% of methoxyflurane biotransformation in the microsomes from imidazole-pretreated rabbits. Thus isozyme 3a or a structurally similar cytochrome P450 seemed to catalyse almost all microsomal metabolism of enflurane. In addition, purified cytochrome P450 3a catalysed the metabolism of enflurane, sevoflurane and methoxyflurane, and the oxidation of these anaesthetics by cytochrome P450 3a was stimulated four-fold by cytochrome b_5, a protein which serves as an alternate source of electrons for some cytochrome P450 reactions.

Enflurane, halothane, isoflurane and methoxyflurane are metabolized *in vivo* by a family of mixed function oxidases termed cytochromes P450. The biodegradation of enflurane results in the formation of fluoride ion, which may cause dose-related nephrotoxicity [1] and the production of organic fluoride metabolites that may, under specific circumstances, induce toxicity [2].

Increased serum concentrations of fluoride ion have been observed following enflurane anaesthesia in a patient taking isoniazid [3]. This observation stimulated studies which confirmed subsequently that isoniazid is an inducer of the *in vivo* and microsomal metabolism of enflurane in man and animals [1, 4]. In rats, enflurane biotransformation is enhanced both following administration of ethanol [5–7] and in the untreated diabetic animal [8]. Phenobarbitone and 3-methylcholanthrene are not inducers of enflurane metabolism [4].

Ethanol, in addition to isonizaid, imidazole and acetone and physiological conditions such as fasting and diabetes, increases the concentration of the ethanol-inducible cytochrome P450, which has been purified from rats and rabbits [9–16]. In addition to being induced by almost identical compounds and by fasting and diabetes, the ethanol-inducible cytochromes P450 from rats and rabbits are also similar in structure and catalytic activity [10]. It was, therefore, not a

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†A preliminary report of these results was published in *Anesthesiology* 1986; 65:A232.

surprise when a cytochrome P450 that immunologically and catalytically resembled the rat and rabbit ethanol-inducible cytochromes P450 was identified in two patients, one receiving isoniazid and the other intoxicated with ethanol [17, 18].

In this study we have shown that the ethanol-inducible cytochrome P450 from rabbits, termed isozyme 3a, oxidizes enflurane, and that microsomes enriched in the ethanol-inducible cytochrome P450 by pretreatment of rabbits with imidazole are also active in enflurane biotransformation.

MATERIALS AND METHODS

The procedure for these studies was approved by the University of California San Francisco Committee on Animal Research. Male New Zealand rabbits (weights 2–2.5 kg) were given tap water containing sodium phenobarbitone 1 mg ml^{-1} for 7 days [19] or an intraperitoneal injection of imidazole 200 mg/kg body weight in aqueous solution adjusted to pH 7.0, on each of 4 days, and killed 24 h after the final administration [20]. Liver microsomes were prepared as described by Haugen and Coon [19] and stored at −80 °C. NADPH-cytochrome P450 reductase was purified from microsomes of phenobarbitone-treated rabbits as described previously [21]. Cytochrome b_5 was purified using the method of Chiang [22] and cytochrome P450 isozyme 3a was purified from microsomes of imidazole-treated rabbits according to the method of Koop and Coon [9]. The preparation was electrophoretically homogeneous (fig. 1) and had a specific content of P450 17.05 nmol/mg of protein.

The metabolism of methoxyflurane, enflurane and sevoflurane was assayed by measuring the production of fluoride ion with an Orion ion-specific electrode. Microsomes and antibodies were preincubated at 30 °C for 30 min before addition of other reagents. The reactions were initiated by addition of 1 µl of the anaesthetic and terminated by heating at 75 °C for 2 min, after a 30-min incubation in a 37 °C water bath, as described previously [21]. Aniline p-hydroxylation was measured by assaying p-aminophenol [23]. The reaction was initiated by addition of aniline to a final concentration of 5 mmol litre^{-1} and terminated by addition of trichloroacetic acid to a final concentration of 10% after incubation for 20 min at 37 °C. The concentration of cytochrome P-450 was measured by the method of Omura and Sato [24] and the concentration of cytochrome b_5 from the absolute spectrum of the ferric protein using an absorption coefficient of 117 mmol litre^{-1} cm^{-1} at 413 nm [25]. Protein concentration was measured by the method of Lowry and colleagues [26].

Synthetic lipids were suspended in water by sonication in a bath-type sonifer (Bransonic 12, Branson Ultrasonic Corp) for 30 min at room temperature. Optical spectra were recorded at room temperature with a Cary 219 spectrophotometer operated in a double-beam mode. Polyacrylamide slab gel electrophoresis was carried out in the presence of sodium dodecyl sulphate (SDS) as described by Laemmli [27]. The antibodies to cytochrome P450 3a were prepared as described previously [9]. Control IgG was isolated from sheep before they were injected with isozyme 3a.

Materials

Imidazole, Tergitol NP-10, D-glucose-6-phosphate (monosodium salt), glucose-6-phosphate dehydrogenase from *Leuconostoc mesenteroides*, β-nicotinamide adenine dinculeotide phosphate (sodium salt), p-aminophenol hydrochloride, cholic acid, polyethylene glycol, DEAE-Cellulose, DEAE-Sepharose, and CM-Sepharose were purchased from Sigma. Hydroxylapatite Ultrogel was obtained from LKB-Produkter. The synthetic lipid dilauroylglyceryl-3-phosphorylcholine was obtained from Calbiochem-Behring. CF1 Cellulose powder was purchased from Whatman. Methoxyflurane containing 0.01% butylated hydroxytoluene was from Abbott Laboratories; enflurane was obtained from Ohio Medical Products; aniline was purchased from Fisher Chemical Co., and redistilled twice before use.

RESULTS

Polyacrylamide gel electrophoresis of microsomes

The hepatic microsomes isolated from control, phenobarbitone- and imidazole-pretreated rabbits were examined by SDS polyacrylamide gel electrophoresis, a technique which resolves proteins primarily on the basis of molecular weight (fig. 1). The microsomes from imidazole-pretreated rabbits had a protein band of increased intensity between phenobarbitone-induced cytochrome P450 isozyme 2, and isozyme 4, induced by polycyclic aromatic compounds [20]. The protein in this band has the same electrophoretic

TABLE I. *Catalytic activities of rabbit liver microsomes: effects of imidazole* v. *phenobarbitone administration (mean (SD)).* n = 6 *(except* †n = *3). Reaction mixtures contained microsomal protein 1 mg ml*$^{-1}$*, Tris acetate 0.1 mol litre*$^{-1}$*, pH 7.4 at 37 °C and an NADPH-generating system* [21]. *$P < 0.0035$; **$P < 0.0000$; ***$P < 0.016$; ****$P < 0.0001$ *compared with control (unpaired* t *test with Bonferroni correction)*

Substrate	Activity (nmol product (nmol of P450)$^{-1}$/30 min) Control	Phenobarbitone-induced	Imidazole-induced
Enflurane	0.95 (0.34)	0.62 (0.39)	2.22 (0.63)*
Methoxyflurane	1.8 (0.88)	19.14 (0.7)**	3.51 (1.11)***
Sevoflurane	1.42 (1.0)	1.16 (0.21)	1.94 (0.41)
Aniline	5.1 (0.17)†	—	15.5 (2.4)****

mobility as the purified isozyme 3a and was presumed to be responsible for enflurane metabolism.

Anaesthetic metabolism by liver microsomes from imidazole-pretreated rabbits

The rates of metabolism of enflurane, sevoflurane and methoxyflurane by hepatic microsomes from untreated, phenobarbitone- and imidazole-pretreated rabbits are compared in table I. The metabolism of the three anaesthetics was increased approximately 2.5-fold above control in microsomes from imidazole-pretreated rabbits. This increase was similar to that observed in the p-hydroxylation of aniline.

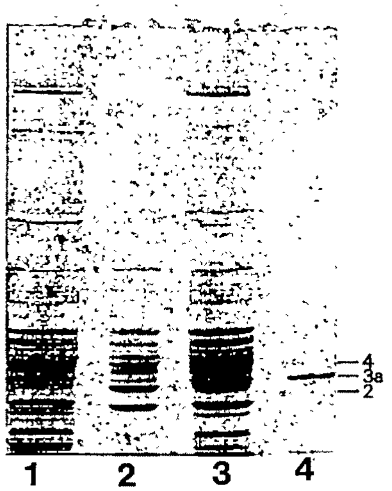

FIG. 1. Polyacrylamide gel electrophoretic pattern of rabbit liver microsomal proteins and cytochrome P450 isozyme 3a. Migration proceeds from top to bottom; proteins with the lowest molcular weight migrate the greatest distance. Wells 1–3 contain 10 μg of microsomal protein from: (1) untreated, (2) phenobarbitone-pretreated and (3) imidazole-pretreated rabbits. Well 4 contains 0.5 μg of cytochrome P450 3a.

Cytochrome P450 3a catalysed oxidation of methoxyflurane, enflurane and sevoflurane and enhancement by cytochrome b_5

Microsomes from imidazole-pretreated rabbits catalysed a greater amount of enflurane metabolism than microsomes from control and phenobarbitone-pretreated animals, suggesting that cytochrome P450 3a may be responsible for enflurane metabolism. To test this hypothesis, cytochrome P450 3a was purified to homogeneity (fig. 1) and its ability to metabolize enflurane was measured. The data in table II demonstrate that cytochrome P450 3a metabolized enflurane, sevoflurane and methoxyflurane, and that this oxidation was stimulated four- to five-fold by cytochrome b_5. In contrast, the metabolism of aniline was inhibited by cytochrome b_5. No anaesthetic metabolism occurred in the absence of cytochrome P450 3a (table III).

Inhibition of the microsomal metabolism of enflurane by antibodies to cytochrome P450

Anti-cytochrome P450 3a polyclonal antibodies, which inhibit only the function of isozyme 3a but not other known isozymes of cytochrome P450, and give a single precipitin line with hepatic microsomes from ethanol-treated rabbits in Ouchterlony double-diffusion experiments [9] were prepared using the method of Koop, Nordblom and Coon [28]. These antibodies were used to determine the extent to which isozyme 3a was responsible for the oxidation of enflurane and methoxyflurane in microsomes from imidazole-

TABLE II. *Effect of cytochrome b_5 on substrate oxidation by cytochrome P450 isozyme 3a in a reconstituted system (containing purified cytochrome P450 3a, NADPH-cytochrome P450 reductase and cytochrome b_5 (each at a final concentration of 1.0 nmol ml^{-1}), dilauroyl phosphatidylcholine (final concentration 100 nmol ml^{-1}), Tris acetate 0.1 mol litre^{-1} pH 7.4 at 37 °C, and an NADPH-generating system* [21]) *(mean (SD)).* n = *3–5.* $^{*}P < 0.043$; $^{**}P < 0.0009$; $^{***}P < 0.019$; $^{****}P < 0.02$ *compared with values obtained in the absence of cytochrome b_5 (unpaired* t *test)*

Substrate	Activity of P450 3a (nmol product (nmol P450)$^{-1}$/30 min)	
	$-b_5$	$+b_5$
Enflurane	0.8 (1.3)	3.8 (0.79)*
Sevoflurane	0.4 (0.17)	2.7 (0.2)**
Methoxyflurane	1.4 (1.35)	6.2 (1.2)***
Aniline	403 (148)	157 (94.5)****

pretreated rabbits. The data in figure 2 illustrate that increasing concentrations of antibodies to cytochrome P450 3a decreased the metabolism of enflurane and aniline in an identical manner. At maximally effective concentrations of antibody, 90 % of the microsomal metabolism of enflurane and aniline was inhibited, suggesting that cytochrome P450 3a catalysed almost all the metabolism of enflurane from imidazole-pretreated animals.

In contrast, O-demethylation of methoxyflurane was decreased by only 40 % under similar conditions (fig. 2). Isozymes of cytochrome P450 other than 3a catalysed approximately 60 % of methoxyflurane oxidation in microsomes from imidazole-pretreated rabbits. The observed decrease in substrate oxidation was not a result of non-specific effect of immunoglobins, as addition of IgG isolated from the serum of pre-immune sheep resulted in unexplained stimulation, rather than diminution in activity.

DISCUSSION

Purification of cytochrome P450 3a increased its specific activity (nmol of product/nmol of P 450/time (tables I and II)) for anaesthetic metabolism two-fold instead of the anticipated four- to five-fold [11]. These results suggest that additional isozymes of cytochrome P450 may catalyse enflurane, sevoflurane and methoxyflurane metabolism in the microsomes of the imidazole-pretreated rabbits. These isozymes are structurally probably related to cytochrome P450 3a because the antibodies to cytochrome P450 3a cause a 90 % inhibition of enflurane metabolism in microsomes.

TABLE III. *Dependence of substrate oxidation on cytochrome P450 (mean (SD)).* n = *3. Reactions as described in table II except that cytochrome P450 3a was omitted from the mixture*

	Oxidation (nmol product/30 min)	
	$-b_5$	$+b_5$
Enflurane	0	0
Sevoflurane	0	0
Methoxyflurane	0.75 (0.8)	1.2 (0.04)

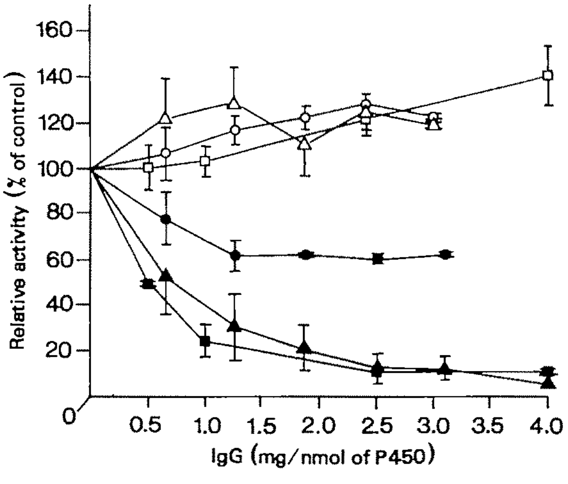

FIG. 2. Effect of anti-3a IgG and pre-immune IgG on the metabolism of enflurane, methoxyflurane and aniline by microsomes from imidazole-pretreated rabbits (mean activity and SD). $n = 3$. Control activity (100 %) obtained in the absence of IgG was fluoride ion 6.61 and 2.5 nmol (nmol of P450)$^{-1}$/30 min for methoxyflurane and enflurane, respectively, and p-aminophenol 0.49 nmol (nmol of P450)$^{-1}$ min^{-1} for aniline. ● = Methoxyflurane, ▲ = enflurane and ■ = aniline, each plus anti-3a IgG. ○ = Methoxyflurane, △ = enflurane and □ = aniline, each plus pre-immune IgG.

In these studies, enflurane metabolism was induced with imidazole, which is a more efficient inducer of cytochrome P450 3a than is isoniazid (447% *v.* 213%) in rabbits [11]. However, in rats, isoniazid is a better inducer [29], although in humans isoniazid induces enflurane defluorination in only 50% of patients taking the drug [1]. It is not known if this is related to the metabolism of isoniazid by fast and slow acetylators, as has been proposed [1], or to variable amounts of the isoniazid-inducible cytochrome P450. The molecular basis of the ability of isoniazid to induce varying amounts of the enflurane metabolizing cytochrome P450 in different species is not known.

What is the clinical relevance of our finding that cytochrome b_5 stimulated anaesthetic metabolism by cytochrome P450 3a? The major *in vivo* function of cytochrome b_5 is to provide reducing equivalents for lipid biosynthesis. In addition, cytochrome b_5 also enhances the cytochrome P450-catalysed metabolism of endogenous substrates such as the prostaglandins and lauric acid by providing the second of the two electrons required for complete oxidation by cytochrome P450 [30]. As the primary source of electrons for cytochrome b_5 and cytochrome P450 is NADH and NADPH, respectively, it is conceivable that *in vivo* cytochrome b_5 regulates the oxidation of certain endogenous substrates by cytochrome P450 in response to intracellular concentrations of NADH and NADPH or, *vice versa*, that the endogenous substrates may modulate the availability of NADH and NADPH. Consequently, anaesthetic metabolism may be regulated by the redox state of the hepatocyte. Alternatively, hepatic anaesthetic metabolism, via its requirement for cytochrome b_5, may interfere with intracellular lipid biosynthetic reactions, thereby adversely affecting hepatocyte function and contributing to the postoperative hepatotoxic effects of anaesthetics.

Our results demonstrate that the ethanol-inducible cytochrome P450 3a from rabbits catalyses the defluorination of enflurane. If the ethanol-inducible cytochrome P-450 in humans is similar to the rabbit and rat ethanol-inducible cytochrome P450 in structure, function and regulatory mechanisms, our data suggest that, in prolonged fasting and untreated diabetes (conditions associated with high serum concentrations of acetone), enflurane defluorination may be enhanced; in addition, ethanol ingestion may increase enflurane biotransformation, depending on the interval between cessation of ingestion and administration of enflurane [7, 31, 32]. Enhanced *in vivo* metabolism of enflurane would be expected following the decline of plasma concentrations of ethanol to non-inhibitory values and before the microsomal decrease of the human homologue of the ethanol-inducible cytochrome P450 [7]. Although clinically significant renal dysfunction is likely to be transient because of the rapid decrease in plasma fluoride ion concentration following enflurane administration, it might be prudent for the clinician to avoid enflurane when anaesthetizing patients with these conditions.

ACKNOWLEDGEMENT

Supported in part by USPHS grant GM 35533.

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Br. J. Anaesth. (1989), **63**, 109–112

MIDAZOLAM ACTS SYNERGISTICALLY WITH METHOHEXITONE FOR INDUCTION OF ANAESTHESIA

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SUMMARY

The induction dose–response of midazolam was compared with the dose–response of its combination with methohexitone sodium and with that of methohexitone alone. Three groups of 60 unpremedicated ASA physical state I or II women undergoing minor gynaecological interventions were studied. The end-point of induction of anaesthesia was inability to open eyes upon command. Dose–response curves were determined for each group with a probit procedure and compared with an isobolographic analysis. Midazolam was found to act in synergism with methohexitone for induction of anaesthesia. Twenty-seven percent ED_{50} *for methohexitone was required in combination with 33% of* ED_{50} *for midazolam to achieve the* ED_{50} *of the combination. This degree of synergism is in agreement with that described in animal research.*

Barbiturates modulate benzodiazepine receptors by enhancing binding of these drugs to the receptor [1–4]. In addition to their intrinsic anaesthetic effect, this should create some degree of synergism. This occurs in rats, with which the righting reflex is used as an end-point for anaesthetic action [5].

Of the barbiturates, methohexitone has recently attracted renewed interest and the present study was designed to test the anaesthetic interaction between midazolam and methohexitone. Following an initial determination of a dose–response curve for each drug, 27% of ED_{50} for methohexitone was administered with increasing doses of midazolam.

PATIENTS AND METHODS

One hundred and eighty women (age 20–50 yr, ASA I or II) admitted for minor gynaecological procedures participated in the study following informed consent. The Institutional Review Board approved the study design.

The dose regimens used for the study are shown in table I. Drugs were injected in a constant volume of 10 ml over 15 s. Two separate injections were administered at an interval of 1 min and the end point of response to verbal command ("open your eyes") was evaluated 3 min after the first injection. In the combination group, midazolam was injected first, and in the other two groups saline was used as placebo. The drugs were labelled only as first and second, so that the administering physician was unaware of their nature. However, studies of the single-drug groups were concluded first, so that the doses for the combination could be planned.

TABLE I. *Dose groups of patients in the study. Mi = Midazolam; Me = methohexitone.* n = *Number of patients*

Midazolam (mg kg^{-1})	Methohexitone (mg kg^{-1})	Mi + Me combination (mg kg^{-1})
0.07 ($n = 10$)	0.3 ($n = 10$)	0.03 + 0.225 ($n = 10$)
0.10 ($n = 10$)	0.5 ($n = 10$)	0.04 + 0.225 ($n = 10$)
0.13 ($n = 10$)	0.7 ($n = 10$)	0.06 + 0.225 ($n = 10$)
0.19 ($n = 10$)	0.9 ($n = 10$)	0.08 + 0.225 ($n = 10$)
0.26 ($n = 10$)	1.1 ($n = 10$)	0.11 + 0.225 ($n = 10$)
0.37 ($n = 10$)	0.15 ($n = 10$)	0.15 + 0.225 ($n = 10$)

The percentage of patients in each dose group

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unable to open the eyes was converted into a probit value and plotted against a logarithmic value for the respective dose. Dose–response curves were determined with the use of probit analysis [6].

To define the type of interaction between midazolam and methohexitone, isobolographic analysis was used (ED_{50} value) [7]. The three calculated ED_{50} values were plotted in the form of an isobologram. Single-drug ED_{50} points were placed on the dose co-ordinates, and the combined ED_{50} point in the dose field representing the doses of each drug contained in the ED_{50} of the combination.

A straight line joining the single-drug ED_{50} points is termed the "additivity line" and deviation of the ED_{50} of a combination to the left indicates synergism. This deviation is measured perpendicular to the additivity line. The standard error of this distance was computed by the method of propagation of error [8], and error estimates from the combined ED_{50} point, in addition to single-drug ED_{50} points, were used. An approximate *t* test used to test the assumption of additivity was obtained as the ratio of measured distance to its standard error [9].

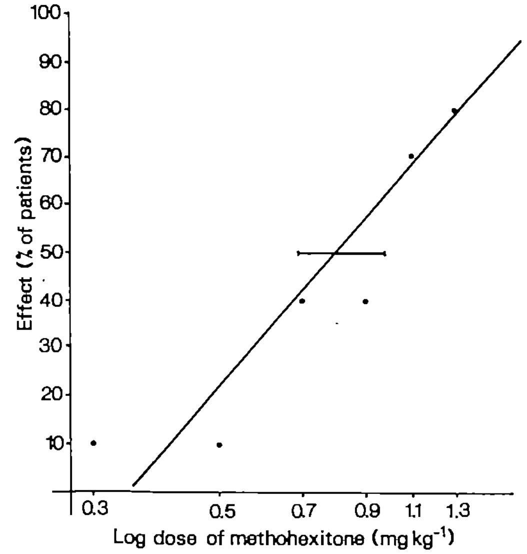

FIG. 1. Methohexitone quantal dose–response curve for induction of anaesthesia. Vertical axis: percentage of patients (on a probit scale) who did not open their eyes in response to the command. Horizontal axis: dose of methohexitone (on a log scale). Each point represents a subgroup of 10 patients at the dose indicated. Horizontal line at the ED_{50} level indicates 95% confidence interval (asymetry is attributable to the log scale).

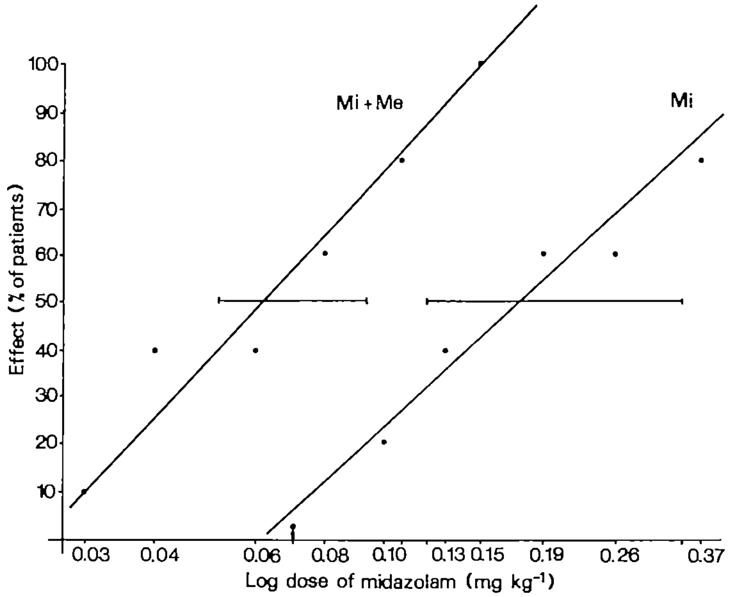

FIG. 2. Midazolam (Mi) quantal dose–response curve for induction of anaesthesia with and without the addition of methohexitone. Mi+Me = dose–response curve for midazolam with the addition of methohexitone 0.225 mg kg^{-1}. Each point represents a subgroup of 10 patients at the dose indicated. Horizontal line at the ED_{50} level indicates 95% confidence interval (asymetry is attributable to the log scale).

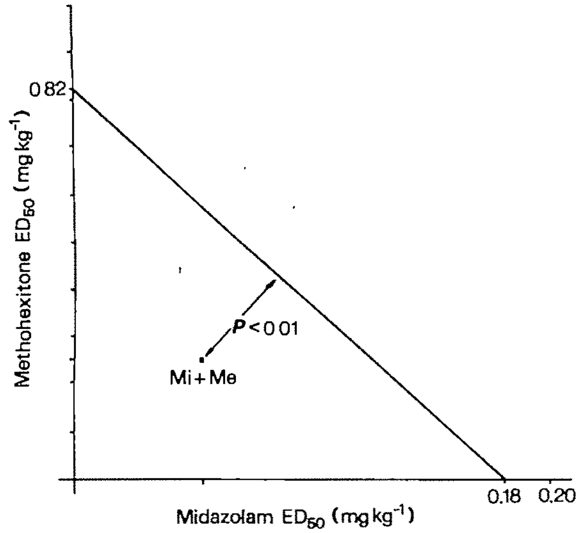

FIG. 3. ED$_{50}$ isobologram for the anaesthetic interaction of midazolam and methohexitone. ED$_{50}$ values indicate the dose that provides the effect in 50% of the patients when each drug was used alone. Mi+Me = ED$_{50}$ value for the midazolam-methohexitone combination. The straight line connecting the single-drug ED$_{50}$ points is an additivity line. P = level of significance of deviation of the combined ED$_{50}$ point to the left of the additivity line, indicating synergism.

RESULTS

The groups were comparable with respect to age and weight. The methohexitone dose-response curve is presented in figure 1. The ED$_{50}$ calculated from this curve is 0.82 mg kg^{-1}. In figure 2 the dose-response of midazolam alone and in combination with methohexitone 0.225 mg kg^{-1} (approximately 25% of the calculated ED$_{50}$) is presented. The displacement of the curve to the left with the combined dose is evident: ED$_{50}$ values were 0.182 mg kg^{-1} and 0.062 mg kg^{-1} for midazolam alone and in combination, respectively.

The difference between the slopes did not reach statistical significance by this method of analysis. However, the midazolam-methohexitone isobologram for ED$_{50}$ doses (fig. 3) reveals that the combined ED$_{50}$ point deviates to the left of the additivity line, indicating synergism ($P < 0.01$). In table II ED$_{50}$ values are presented as the sum of fractional doses given from each drug alone with that given in the combination, and this also demonstrates synergism by the smaller fractional dose needed for the same effect with combined administration.

DISCUSSION

The methohexitone ED$_{50}$ found in this study (0.82 mg kg^{-1}) is in agreement with that (0.8 mg kg^{-1}) reported by Clarke and colleagues [10] and with others [11–13], despite the differences in methodology and end point for anaesthesia. The ED$_{50}$ of midazolam found in several other studies was not constant and varied from 0.13 mg kg^{-1} to 0.19 mg kg^{-1} for the same end point [14–16]. These values are in agreement with the present study.

The combination of the two drugs gave an ED$_{50}$ which was 0.61 of the fractional dose needed for ED$_{50}$ from each drug when given alone. Thus 27% of the ED$_{50}$ of methohexitone reduced by 66% the midazolam required to achieve anaesthesia. This degree of synergism is close to that found in rats for midazolam and thiopentone when the righting reflex was used as end point [5]. The calculated fractional dose for combined administration in rats was 2.6 times lower than the single-drug fractional dose, compared with 1.63 in our patients. In a recent study we

TABLE II. *Midazolam-methohexitone anaesthetic interaction. Mi = midazolam alone; Me = methohexitone alone; Mi+Me = combined administration. † Ratio of single-drug fractional dose to combined fractional dose*

	Equi-effective doses (ED$_{50}$) of midazolam-methohexitone combination					
	Midazolam component		Methohexitone component			
Group	Fraction of ED$_{50}$	Dose (mg kg^{-1})	Fraction of ED$_{50}$	Dose (mg kg^{-1})	Sum of fractional doses	Ratio†
Mi	1.00	0.18	—	—	1.0	—
Mi+Me	0.34	0.06	0.27	0.225	0.61	1.63
Me	—	—	1.00	0.82	1.0	—

demonstrated [17] that midazolam and thiopentone act synergistically in humans, with a reduction of the fractional dose by 2.

It is reasonable to assume that the same magnitude of synergism between barbiturates and midazolam for both humans and rats indicates that a similar mechanism is involved, thereby suggesting that the rat may be a good model for investigation of synergism in man. If a pharmacokinetic mechanism for this synergism is excluded it may be speculated that the receptors for benzodiazepines and barbiturates (probably together with GABA receptors) are parts of a supramolecular complex in which each site, when occupied, modulates the others [18]; with regard to methohexitone and midazolam, the former enhances the binding and effect of the latter.

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Br. J. Anaesth. (1989), **63**, 113–115

THE AUDITORY EVOKED RESPONSE AS AN INDICATOR OF AWARENESS

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SUMMARY

The latency of the early cortical wave Nb of the auditory evoked response (AER) was compared with responses to Tunstall's isolated forearm test, while the concentration of nitrous oxide was progressively reduced during light anaesthesia in seven patients. A threshold Nb latency of 44.5 ms was chosen to discriminate between an early cortical AER containing three waves and that with two waves of longer latency. When Nb latency decreased below this threshold, four of the patients has positive responses, indicating awareness. The addition of a volatile anaesthetic abolished any response, and increased Nb latency to more than 44.5 ms. The three wave AER pattern, therefore, is associated with a depth of anaesthesia at which awareness occurs.

Previous studies using the auditory evoked response (AER) to investigate depth of anaesthesia [1,2] demonstrated changes in the early cortical AER with increasing concentrations of anaesthetic agents. These studies began with a background anaesthetic of 70% nitrous oxide in oxygen. Immediately after induction of anaesthesia and tracheal intubation, a period which is associated with a risk of awareness, the AER displayed a characteristic pattern. This consisted of three positive waves occurring between latencies of 15 and 100 ms. These correspond with the waves Pa to Pc [3]. Adding the test anaesthetic increased the latencies of the waves to the extent that only two were recorded in the same time window. Deepening the anaesthetic further reduced amplitudes and increased latencies.

Using discriminant function analysis on the various latencies and amplitudes in 36 patients studied previously, the latency of the early cortical wave Nb emerged as the best feature distinguishing the "three wave" AER pattern (Nb latency less than 44.5 ms) from the "two wave" pattern (Nb latency greater than 44.5 ms). In these previous studies, no attempt had been made to elicit a response, as the patients were paralysed and subsequently anaesthetized deeply, and had no recall afterwards. This does not preclude the possibility that the patients were aware or very lightly anaesthetized when the three high amplitude waves were seen.

In the present study, we used Tunstall's isolated forearm technique [4], together with the AER, to test the hypothesis that Nb latencies of less than 44.5 ms are associated with very light anaesthesia and awareness.

METHODS AND RESULTS

The study had Hospital Ethics Committee approval. Seven elective surgical patients agreed to be studied in a period after induction of anaesthesia and before surgery. The aims of the study and the use of the isolated forearm method to detect awareness were explained fully.

Premedication with morphine and atropine was given 1 h before anaesthesia, which was induced with sodium thiopentone i.v. and maintained by

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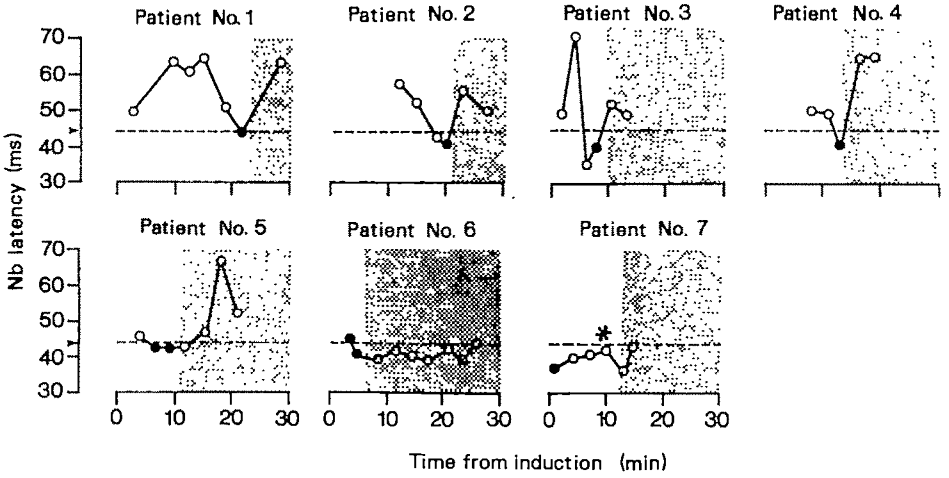

FIG. 1. Nb latency (ms) plotted against time from induction of general anaesthesia. Positive responses of the isolated arm to verbal command are shown as closed circles, a spontaneous movement is shown by an asterisk. The nitrous oxide concentration was reduced gradually to the point where the shading indicates that an inhalation agent was administered. Nb latency of 44.5 ms is indicated by the horizontal line.

70% nitrous oxide in oxygen. A pneumatic tourniquet on the dominant arm was inflated to a value greater than systolic arterial pressure and pancuronium or vecuronium was given via the other arm, for tracheal intubation [4]. At 2–3 min intervals the patient was asked to squeeze and release the investigator's fingers (an unequivocal response).

Corresponding AER recordings were made in response to clicks (Telephonics TDH 39P Headphones, 6 Hz, 70 dB above the average hearing threshold) using silver–silver chloride electrodes (mastoid with vertex as a reference). The signals were amplified by 100 dB at a frequency response of 25–3600 Hz using purpose-built amplifiers. The EEG signals were recorded on FM tape for subsequent analysis using a Datalab DL 4000 averager.

The concentration of nitrous oxide was reduced gradually to 50% (inspired) or until there was a response, whichever happened first. At that point 1–2% inspired enflurane was given. Readings were continued until the start of surgery.

In patients Nos 1–4 there was an initial period in which no patient movement occurred, followed by a positive movement on command. This constituted an unambiguous end-point (fig. 1). Responses were seen in patients only when Nb latency was 44.5 ms or shorter. After a volatile agent was added to the anaesthetic, patients no longer responded and the Nb latencies increased above the 44.5-ms threshold.

Patients Nos 5–7 gave equivocal responses. For example, patient No. 5 developed hand clenching approximately 7 min after induction of anaesthesia (previously giving no response to command). The Nb latency at the time was less than 44.5 ms, and when the inhalation agent was added it increased above this value and the clenching ceased. Hand movements occurred immediately following induction of anaesthesia in patients Nos 6 and 7. In these two, most of the Nb latencies recorded were less than 44.5 ms. In patient No. 6 the inhalation agent did not change Nb latency. Although patient No. 7 responded only once, clinically his anaesthesia became progressively lighter, and both arms moved at the point indicated in the figure by an asterisk, at which point the inhalation agent was given. On recovery, none of the patients remembered any event following induction of anaesthesia.

COMMENT

The data of patients Nos 1–4 demonstrated an association between short Nb latency and awareness. Patients Nos 5–7 demonstrated signs of light anaesthesia (some arm movements did occur) also at Nb latencies less than 44.5 ms. Considering the limitations of the clinical situation and the problems with the isolated forearm technique described below, the results lead us to conclude that there are characteristic patterns in the AER which indicate potential awareness.

When applying this technique to monitor patients during elective Caesarean section, the authors (who had no control over the anaesthetic) found few positive responses using the isolated arm technique. Following delivery, Nb latencies of less than 44.5 ms, suggesting awareness, were seen almost always in patients anaesthetized with nitrous oxide, oxygen and morphine. In others who received enflurane, Nb latencies invariably exceeded 44.5 ms.

Our findings are in line with those of Russell [5] who showed that 44% of patients anaesthetized with nitrous oxide and fentanyl alone showed positive or equivocal responses during isolated arm testing, compared with only 7% in patients receiving an infusion of etomidate. He has also suggested [6] that the isolated forearm technique may underestimate the incidence of awareness because, even when electrical nerve stimulation showed that a response should be possible, some patients wished to respond but were unable to.

A characteristic AER pattern identified by Nb latencies less than 44.5 ms was associated with both a high incidence of responses of the isolated arm to verbal command, and with very light anaesthesia. Further studies are necessary to develop the technique of AER pattern recognition and to allow on-line analysis if it is to provide a clinical indicator of awareness.

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Br. J. Anaesth. (1989), **63**, 116–120

EXTRADURAL ANALGESIA IN THE INTRAPARTUM MANAGEMENT OF A PATIENT WITH PULMONARY HYPERTENSION

K. J. POWER AND A. F. AVERY

Primary pulmonary hypertension is a rare disorder characterized physiologically by inappropriately increased pulmonary artery pressure (e.g. a pressure greater than 30/15 mm Hg at a resting cardiac output of 5 litre min^{-1}) resulting from an increase in pulmonary vascular resistance [1].

The differentiation of primary pulmonary hypertension from secondary causes such as thromboembolic disease may be difficult and it has been suggested that the definitive diagnosis of primary pulmonary hypertension is appropriate only at postmortem [2]. Histologically there is medial hypertrophy of the arteriolar wall of unknown aetiology. The disease is rare; 80% of those affected are women, the majority of whom are of child bearing age [3]. It is not clear if pregnancy itself contributes primarily to the development of pulmonary hypertension or if the increased cardiovascular demands of pregnancy unmask a pre-existing condition [4].

There have been five reports of the intrapartum management of these patients, four of whom died early in the puerperium [5–9]. We describe another case report in this paper.

CASE REPORT

A 27-yr-old primigravida attended the antenatal clinic at 9 weeks gestation. She was apparently healthy and gave no history of symptoms referable to the cardiovascular system. She noted some dyspnoea at 22 weeks gestation, but presented to an E.N.T. surgeon at 26 weeks gestation with a hoarse voice, at which time a left recurrent laryngeal nerve palsy was diagnosed. Her dyspnoea worsened and a cardiologist's opinion was sought.

SUMMARY

We describe the intrapartum management of a patient with severe pulmonary hypertension using extradural analgesia with a low dose of 0.125% bupivacaine and fentanyl 20 μg ml^{-1} by continuous infusion at a rate of 2.5 ml h^{-1}. This provided effective analgesia and haemodynamic stability. The importance of continuous direct measurement of pulmonary artery pressure is emphasized.

By 30 weeks gestation the patient was dyspnoeic on minimal exertion, with slight central and peripheral cyanosis. Systemic arterial pressure was 100/60 mm Hg and the jugular venous pressure was increased to 10 cm with prominent a and v waves. Clinically, there was right ventricular hypertrophy and chest auscultation revealed a loud pulmonary component to the second sound, a fourth heart sound and a pansystolic murmur at the left sternal edge compatible with tricuspid regurgitation.

The ECG demonstrated sinus rhythm with right atrial and right ventricular hypertrophy. Chest radiography revealed moderate enlargement of the heart and main pulmonary arteries possibly compatible with normal pregancy. Echocardiography demonstrated a large right ventricle but with no evidence of intracardiac shunt. The peak flow of tricuspid regurgitation was used to estimate indirectly the pulmonary artery systolic pressure at 46 mm Hg. A ventilation–perfusion scan demonstrated a segmental perfusion defect in the left upper zone compatible with a pulmonary embolus.

Despite the findings of the ventilation–perfusion

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scan, it was felt that the most likely diagnosis was primary pulmonary hypertension rather than pulmonary hypertension secondary to thromboembolic disease, although the precise differentiation between these two is notoriously difficult. Pulmonary angiography and direct pressure measurements were not made at this stage, as it was felt that this could be potentially hazardous while contributing little to practical management. Anticoagulation was commenced with heparin and the patient was maintained on bed rest and continuous oxygen therapy. The arterial oxygen tension improved from 8.9 kPa to 11–12 kPa with $F\text{I}_{\text{O}_2}$ 0.24.

The obstetricians recommended that pregnancy proceed as near to term as possible and that delivery should be by the normal vaginal route. Extradural analgesia was offered, not only to provide adequate analgesia, but also to attenuate the adverse cardiovascular consequences of labour.

Subsequently, the patient went into spontaneous labour at 38 weeks gestation and the heparin infusion was stopped. Shortly afterwards, a flow directed pulmonary artery catheter (7-French gauge) was introduced via the right internal jugular vein for direct measurement of pulmonary artery pressures. "Wedge" pressure readings were not taken regularly because of reports in the literature citing the dangers of this procedure in this group of patients [10]. However, in the event of cardiovascular instability occurring, the facility was available for direct measurement of cardiac output and pulmonary and systemic vascular resistances.

When the cervix was dilated 4 cm, blood coagulation was assessed and extradural block performed at the L2/3 space using a 16-gauge needle. Following a test dose of 1.5% lignocaine 3 ml, a 4-ml loading dose was given of a solution containing fentanyl 20 μg ml^{-1} in 0.125% bupivacaine. Subsequently, analgesia was maintained with an infusion of this solution at a rate of 2.5 ml h^{-1}. Satisfactory analgesia was obtained with a sensory level at T10 on the right and T9 on the left.

Changes in pulmonary artery pressure are shown in figure 1. There was an increase in pulmonary artery pressure from 88/36 to 102/61 mm Hg with increasing labour pains and with a subsequent decrease to 82/56 mm Hg when the extradural block was established. During the course of the infusion, systemic arterial pressure decreased from 100/70 to 90/70 mm Hg.

Labour progressed well and, 1 h after the extradural infusion was commenced, the cervix was dilated fully, and an elective forceps delivery was performed to avoid the haemodynamic effects

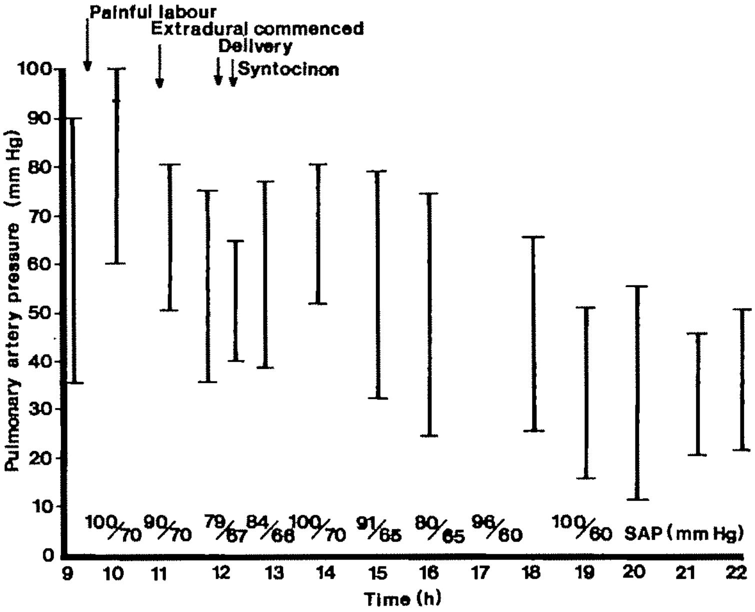

FIG. 1. Changes in pulmonary artery pressure during the course of the labour.

of "pushing". Analgesia was satisfactory for the forceps delivery of a live infant in good condition weighing 2.76 kg. Following delivery, controlled blood loss of 350 ml was permitted in order to attenuate the effects of autotransfusion to the mother from the utero–placental bed. At the end of this period, pulmonary artery pressure was 65/40 mm Hg and it increased to 76/40 mm Hg with the administration of syntocinon 10 units, given cautiously to terminate blood loss.

Throughout labour, solutions of salbutamol, isosorbide dinitrate, dopamine, dobutamine and phenylephrine were available to treat any episode of severe haemodynamic instability.

Following delivery, the patient was transferred to the intensive care unit where the pulmonary artery catheter was removed after 10 h, at which time pulmonary artery pressure had stabilized to approximately 60/40 mm Hg. The early puerperium was uneventful, although there was no regression of the symptoms of pulmonary hypertension.

The patient was discharged after 2 weeks. However, some 4 weeks later, she was readmitted with an exacerbation of dyspnoea resulting in transfer to a regional referral centre where, unfortunately, she suffered a fatal cardiorespiratory arrest while awaiting assessment for possible heart–lung transplantation. Permission for postmortem was not obtained.

DISCUSSION

Primary pulmonary hypertension has a mortality rate in excess of 50% during pregnancy [1]. It may be defined as a pulmonary artery pressure in excess of 30/15 mm Hg associated with right ventricular hypertrophy, and eventual progression to a low, fixed cardiac output state. Circulatory collapse may result from a reduction in venous return or a decrease in systemic vascular resistance, both of which may result from uncontrolled vasodilatation. Because of these considerations, spinal and extradural analgesia have been avoided traditionally in this group of patients [12].

Mangano [12] has advocated the use of systemic opioids and inhalation analgesia, but there are disadvantages to this approach, as the quality of analgesia is unreliable and opioids may cause maternal hypercapnia, increasing further the pulmonary vascular resistance. In addition, nitrous oxide has been shown to increase pulmonary vascular resistance, particularly in patients with pre-existing pulmonary hypertension [13]. Nevertheless, the pain and stress of labour tend to cause dangerous increases in pulmonary vascular resistance, increasing the work of the heart and precipitating heart failure.

During the course of normal labour, cardiac output may increase by 50% during contractions. In addition, 300–500 ml of blood is expelled into the circulation during each contraction, causing a transient increase in CVP, arterial pressure and cardiac output [14]. Cardiac output is increased maximally, by up to 80% immediately postpartum as a result of placental auto-transfusion. Thus, despite the inherent dangers of an extradural block, there are advantages from providing optimal analgesia in conjunction with controlled vasodilatation to accommodate autotransfusion.

Our objective in the management of this patient was to utilize the analgesic properties of extradural fentanyl [15] to permit a reduction in the dose of bupivacaine and so reduce the extent of sympathetic block. The use of a continuous infusion should obviate the need for "top-ups" which may be associated with episodes of haemodynamic instability.

Dopamine and dobutamine were available as inotropes, although high doses may impair uterine blood flow [16]. Salbutamol was available also, as there are reports of its selective action in dilating the pulmonary vasculature whilst maintaining cardiac output, albeit with tachycardia (17). We would have treated excess hypotension caused by sympathetic block with phenylephrine. Isosorbide dinitrate was available to increase venous capacitance in the event of an increase in pulmonary artery pressure consequent upon an increased venous return.

Other drugs of potential value include calcium channel blockers and the potent vasodilator, prostacyclin. Crevey and colleagues [18] demonstrated an 11% decrease in mean pulmonary artery pressure with i.v. diltiazem, whilst similar results have been reported with verapamil [19] and sub-lingual nifedipine [20]. More recent reports suggest a promising role for prostacyclin. Jones, Higgenbottam and Wallwork [21] demonstrated an 18% decrease in mean pulmonary artery pressure in 10 patients awaiting heart–lung transplantation. However, there were large and variable decreases in the systemic vascular resistance.

A review of the literature has revealed four reports of the use of extradural analgesia; three of the four patients died early in the puerperium from episodes of intractable heart failure [5–8]. Three of the four required pharmacological intervention for haemodynamic instability. It has been claimed that the use of nitroglycerin may provide preferential pulmonary vasodilatation whilst maintaining systemic pressures [22]. There were no reports of episodes of severe hypotension because of peripheral vasodilatation resulting from high sympathetic block.

A report from Japan [8] illustrated the danger of accelerating labour with oxytocin. The painful augmented contractions resulted in a sudden, marked increase in pulmonary artery pressure before extradural analgesia was established.

There is one report of intrathecal morphine being used to provide effective analgesia during labour [9]. However, severe pruritus post partum necessitated naloxone infusion.

Consideration must be given to the technique of choice for Caesarean section. Roessler and Lambert [23] reported an initially satisfactory outcome using extradural anaesthesia for a patient undergoing elective Caesarean section. The pulmonary artery pressure of 62/40 mm Hg was less severe than in some other patients described and a successful block was achieved using 0.5% bupivacaine 22 ml. General anaesthesia is undoubtedly hazardous. Coughing or straining at induction may increase intrathoracic pressure and pulmonary vascular resistance, whilst the haemodynamic responses to laryngoscopy and intubation could be equally hazardous. The use of larger doses of anaesthetic agents to suppress these responses may enhance myocardial depression, although barbiturates and opioids have little direct effect on pulmonary vascular resistance [24]. Isoflurane may be the agent of choice, as a recent report showed a significant reduction in pulmonary artery pressure and pulmonary vascular resistance in a patient with primary pulmonary hypertension undergoing ventilation with 0.5–1 % isoflurane [25]. The increase in pulmonary vascular resistance produced by nitrous oxide [13] arguably makes the use of an air–oxygen mixture preferable.

The outcome of this and other cases does not permit conclusions to be drawn on the optimum management of this condition. The prognosis is so poor that, if the condition is diagnosed early in pregnancy, termination is indicated. However, early diagnosis may not always be possible.

The early successful outcome in this patient, associated with haemodynamically stable labour, suggests that the combination of an opioid with a local analgesic drug given by the extradural route may result in a local analgesic sparing effect, thereby improving haemodynamic stability without compromising the quality of analgesia.

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Br. J. Anaesth. (1989), **63**, 121–124

CAESAREAN SECTION AT 27 WEEKS GESTATION WITH REMOVAL OF PHAEOCHROMOCYTOMA

P. M. HOPKINS, R. MACDONALD AND G. LYONS

SUMMARY

We describe the anaesthetic management of a 31-yr-old woman undergoing combined Caesarean section and removal of phaeochromocytoma during the 27th week of pregnancy. The technique used (general anaesthesia with extradural block) provided good operating conditions and a relatively stable haemodynamic state.

We describe a patient in whom phaeochromocytoma was diagnosed in the 26th week of pregnancy. Combined Caesarean section and removal of phaeochromocytoma was undertaken during the 27th week of pregnancy for obstetric indications. The use of extradural block for phaeochromocytoma surgery has been proposed by Bromage and Millar [1], and by Cousins and Rubin [2], but has not gained widespread acceptance because of the theoretical possibility of increased sensitivity to circulating catecholamines during extradural block [3]. This is the first report of extradural block used in combined Caesarean section and removal of phaeochromocytoma.

CASE REPORT

A 31-yr-old woman was transferred to our unit in the 26th week of her third pregnancy, with a 3-month history of intermittent headaches, flushing and dizziness. She had been hypertensive since the 12th week of pregnancy. Labetalol 200 mg 8 hourly and methyldopa 250 mg 8 hourly did not control her arterial pressure. Urinary concentrations of methylated amine were suggestive of phaeochromocytoma.

On her admission to hospital, arterial pressure was 160/100 mm Hg, and fundoscopy revealed grade II hypertensive changes. Plasma urea and electrolyte concentrations, blood count and clotting screen were normal. Clinically, there was the possibility of a small placental abruption. An abdominal ultrasound scan showed a fetus of 24-week size (indicating intrauterine growth retardation) with a low-lying placenta, and a 7 cm × 4 cm × 4 cm left adrenal mass. The diagnosis of a noradrenaline-secreting phaeochromocytoma was confirmed by increased plasma concentrations of noradrenaline (normal concentrations of adrenaline and dopamine in urine and plasma).

Phenoxybenzamine was commenced (10 mg daily, increasing by 10 mg each day) and paroxysmal hypertension controlled with i.v. labetalol. When her condition had stabilized, CT scan confirmed that the left adrenal gland was the sole tumour site and there was no evidence of malignancy. After discussion amongst obstetricians, surgeons, anaesthetists and paediatricians it was decided to undertake combined Caesarean section and removal of phaeochromocytoma at 30 weeks gestation.

Five days after admission, fetal biophysical profile revealed no end-diastolic flow in the umbilical and arcuate arteries. The cardiotocograph at this stage was normal, but the following day showed some decelerations. It was decided to combine Caesarean section and tumour removal within 24 h. Medication at this time comprised labetalol 400 mg 12 hourly and phenoxybenzamine 40 mg 12 hourly (AP 170/100 mm Hg). The patient was transferred to the Intensive Care Unit where radial arterial and peripheral venous cannulation was performed. A Gould 7.5-French gauge thermodilution catheter (SP 5507H) was used to cannulate a pulmonary artery via the right internal jugular vein, and its position was confirmed with chest x-ray. During insertion of the

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TABLE I. *Preoperative haemodynamic data*

Heart rate (beat min^{-1})	104
Systemic arterial pressure (mm Hg)	
Systolic	172
Diastolic	103
Mean	128
Pulmonary arterial pressure (mm Hg)	
Systolic	19
Diastolic	13
Mean	15
Pulmonary wedge pressure (mm Hg)	10
Cardiac output (litre min^{-1})	6.7

pulmonary artery catheter, systemic arterial pressure increased to 230/120 mm Hg. Diazemuls 10 mg, labetalol 100 mg, phenoxybenzamine 100 mg and practolol 10 mg were given i.v. to control arterial pressure. Baseline haemodynamic data were recorded (table I). Ranitidine 150 mg and temazepam 20 mg were given by mouth. Oxygen 4 litre min^{-1} by mask and 0.18 % saline in 4% dextrose i.v. at a rate of 140 ml h^{-1} were administered overnight.

Premedication was administered 2 h before operation and comprised metoclopramide 10 mg, ranitidine 150 mg and diazepam 20 mg by mouth, in addition to the morning doses of labetalol and phenoxybenzamine. In the operating theatre, the patient's lungs were preoxygenated for 5 min and phenoperidine 2 mg given i.v. Following induction of anaesthesia with thiopentone, cricoid pressure was applied, vecuronium 10 mg administered and the lungs ventilated gently with 1 % isoflurane and 50 % nitrous oxide in oxygen via a mask for 3 min before tracheal intubation. General anaesthesia was maintained with isoflurane and 65 % nitrous oxide in oxygen. Neuromuscular block was provided by an infusion of vecuronium. A lumbar extradural catheter was sited and a test dose of plain 1 % lignocaine 4 ml given. Plain 0.5 % bupivacaine 10 ml was administered. Caesarean section was performed when the extradural block was assumed to have taken effect. A male infant (weight 815 g) was delivered with Apgar scores of 2, 7 and 10 at 1, 5 and 10 min, respectively. He was transferred to the neonatal unit and has since been discharged home.

At completion of Caesarean section, plain 0.5 % bupivacaine 15 ml was administered. Subsequently, a left subcostal incision was made and the tumour excised. Blood loss for the combined procedures was approximately 500 ml.

Throughout the procedure, a record was made of heart rate, arterial pressure and cardiac output, and potential influences on these were noted. Cardiac output was measured using a Mennon Horizon 2000 cardiac output computer, which utilizes the thermodilution technique. For each recording of cardiac output, the mean of three measurements was taken. After operation, the patient was returned to the Intensive Care Unit and pain relief provided with extradural morphine 3 mg and an extradural infusion of plain 0.25 % bupivacaine 10 ml h^{-1} to ensure good analgesia. Phenoxybenzamine was discontinued, and the labetolol reduced gradually over the next 2 days. The patient remained in the Intensive Care Unit for the first 24 h after operation, and was then transferred to the maternity unit. She was discharged home on the 12th day after operation.

DISCUSSION

This patient presented with combined problems of Caesarean section and a noradrenaline-secreting phaeochromocytoma. Preoperative preparation with α-adrenergic blocking drugs (most commonly phenoxybenzamine) is regarded generally as the major influence in decreasing the perioperative morbidity in patients undergoing surgical excision of a phaeochromocytoma [4]. We considered the addition of extradural block because, even after pretreatment with phenoxybenzamine, many patients undergoing phaeochromocytoma surgery have marked hypertensive responses [5].

Our aim was to achieve a safe, smooth induction and tracheal intubation with minimal effects on arterial pressure and heart rate, while preventing the usual problems which may occur during induction of anaesthesia in the pregnant patient. The use of opioids to reduce the hypertensive response to intubation may compromise the newly born infant, but the neonatologists had indicated that it was to undergo elective ventilation because of immaturity and consequently naloxone was not given. Although thiopentone, theoretically, may release catecholamines secondary to histamine release [6], it has been shown to cause a decrease in plasma catecholamine concentrations [7] and, because it provides the smoother induction, we preferred to use it, rather than etomidate.

Rapid sequence induction is usual in pregnant patients, but it has been suggested that suxamethonium should be avoided in phaeochromocytoma because of its autonomic side-effects and the theoretical possibility of mechanical stimulation of the tumour by fasciculations [5]. Cardiac arrhythmias have been reported also when the drug was used as an aid to intubation in phaeochromocytoma patients [8]. As our patient was only 26 weeks pregnant, it was felt that the risks of suxamethonium outweighed the risks of inhalation and a non-depolarizing neuromuscular blocker was used with cricoid pressure for tracheal intubation. Vecuronium was chosen because it has been shown, in association with phaeochromocytoma, to cause only small increases in plasma catecholamine concentrations, without changes in cardiovascular variables [9].

The α-blockade achieved in our patient was not sufficient to prevent marked hypertension in response to stress, as seen during the insertion of the pulmonary artery catheter. The β-blockade achieved with labetalol was considered also to be inadequate as indicated by tachycardia at rest. These observations made easier the decision to use an extradural block.

When Caesarean section is combined with removal of phaeochromocytoma, it is important to reduce catecholamine secretion produced by humoral factors, as high concentrations before delivery impair uterine blood flow. Standard practice is to minimize effects with deep general anaesthesia and vasodilators. Deep general anaesthesia predisposes to cardiovascular collapse, both during and after tumour removal; little is known of the effect of phentolamine on uterine blood flow and the fetus, and sodium nitroprusside may reduce uterine blood flow [10] and cause fetal hypotension [11] and fetal cyanide toxicity [12, 13].

Extradural analgesia, producing total sympathetic blockade, reduces catecholamine secretion in non-pregnant patients undergoing removal of phaeochromocytoma [1, 2]. We were unable to test the effective level of the block, but it is unlikely that total sympathetic block was produced with the volumes of bupivacaine used. This would support the view of Stonham and Wakefield [14], that extradural block inhibits increases in arterial pressure by deafferentation rather than by sympathetic block.

In their comparison of four anaesthetic techniques for resection of phaeochromocytoma, Roizen and colleagues [4] concluded that regional anaesthesia provided no benefits over general anaesthetic techniques. However, their results show that two of seven patients in the regional anaesthesia group required vasodilators during operation whilst all 21 patients given only general anaesthesia did so, and insufficient cardiovascular data were presented to substantiate their conclusions. In our patient arterial pressure was remarkably stable until a few minutes before the tumour was dissected completely free. There was a significant period during which tumour manipulation occurred, with minimal hypertension. The total dose of vasodilator used comprised only 0.5 mg of sodium nitroprusside.

Mihm [15] found little correlation between right and left atrial filling pressures during surgery for phaeochromocytoma, irrespective of previous evidence of congestive cardiac failure. This suggests that pulmonary artery catheterization is advisable during phaeochromocytoma surgery. Cardiac output remained particularly stable throughout the procedure, and the administration of extradural bupivacaine had no deleterious effects.

We have demonstrated that the combination of an extradural block with general anaesthesia was associated with relatively stable arterial pressure and no adverse effects on cardiac output, in a patient undergoing Caesarean section and removal of phaeochromocytoma. We suggest that the use of the combined technique of general with extradural anaesthesia may have a place in the management of phaeochromocytoma with Caesarean section.

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Br. J. Anaesth. (1989), **63**, 125–127

HYPOTENSION AND BRADYCARDIA FOLLOWING SUPERIOR LARYNGEAL NERVE BLOCK

J. R. WILES, J. KELLY AND S. M. MOSTAFA

SUMMARY

Severe hypotension and bradycardia occurred in two patients after superior laryngeal nerve block for awake tracheal intubation. Both patients required treatment with anticholinergic drugs and i.v. infusions and made a good recovery.

Awake tracheal intubation using the fibreoptic laryngoscope is a valuable technique for management of patients with severely restricted neck movement or abnormal anatomy of the larynx [1]. Local anaesthesia for awake intubation may involve the use of superior laryngeal nerve block in conjunction with translaryngeal injection of local anaesthetic, or a "spray as you go" technique [2].

We described a previously unreported complication following block of the superior laryngeal nerve in patients undergoing awake tracheal intubation.

CASE REPORTS

Patient No. 1

A 40-yr-old male (weight 75 kg) with severe ankylosing spondylitis was admitted to hospital for elective right hip replacement. He had bilateral fixed flexion deformities of the hips and virtually no movement of the spine. Examination of the mouth revealed a full set of teeth and restricted mouth opening. Tracheal intubation using a conventional technique was considered impossible. We decided, therefore, to examine his upper airway under local anaesthesia using a fibreoptic laryngoscope.

The patient was premedicated with diazepam 10 mg and glycopyrrolate 0.3 mg i.m. 1 h before operation. In the anaesthetic room an i.v. infusion of Hartmann's solution was commenced and arterial pressure and electrocardiogram were monitored. In a sitting position he was given 4% topical lignocaine 6 mg kg^{-1} via an Acorn nebulizer with a mouth piece. The nose was sprayed with 4% cocaine 1.5 mg/kg body weight. A fibreoptic laryngoscope was passed through the nose and nasopharynx, and a good view of the vocal cords was obtained easily.

One week later the patient was scheduled for a right Charnley Arthroplasty. He was given the same premedication and i.v. infusion. Arterial pressure was 120/80 mm Hg and the heart rate 80 beat min^{-1}. Inhalation of nebulized lignocaine was commenced and nasal cocaine spray applied. A right superior laryngeal nerve block was performed using 2% lignocaine 2 ml with adrenaline 1:100000. Following completion of the injection, the patient became pale and sweaty. Heart rate decreased to less than 50 beat min^{-1} and arterial pressure to 80/60 mm Hg. He was placed supine, given atropine 0.6 mg i.v. and the rate of the i.v. infusion was increased. Five minutes later, arterial pressure was 120/70 mm Hg and heart rate was 90 beat min^{-1}. His colour returned to normal and sweating stopped.

A left superior laryngeal nerve block was performed, without incident. Local anaesthesia of the airway was successful and awake nasotracheal intubation was performed. Thereafter, general anaesthesia and surgery were uneventful.

Three months later the patient was admitted for a left Charnley Arthroplasty. He was given a similar premedication and preparation. Again, following the second superior laryngeal nerve block he became hypotensive (80/50 mm Hg) and developed bradycardia (45 beat min^{-1}). He was given atropine 0.6 mg and Hartmann's solu-

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tion 1 litre i.v. Approximately 5 min later, arterial pressure and heart rate returned to pre-induction values. Local anaesthesia was continued. Tracheal intubation, general anaesthesia and surgery were uneventful.

Four days later his recently inserted hip prosthesis dislocated and required reduction under anaesthesia. Awake tracheal intubation was carried out uneventfully.

Patient No. 2

The second patient was a 60-yr-old, 80-kg non-insulin dependent diabetic man with a large fixed submandibular mass, admitted to hospital for endoscopy and biopsy. He received glibenclamide 5 mg daily. Laryngeal tomography showed a tumour invading the right pyriform fossa, and encroaching on the airway. We decided to intubate the trachea with the patient awake, using a fibreoptic laryngoscope. Premedication comprised diazepam 10 mg and glycopyrrolate 0.3 mg. In the anaesthetic room an i.v. infusion of normal saline was commenced. Arterial pressure was 135/85 mm Hg and heart rate 90 beat min^{-1}. Nebulized topical lignocaine and cocaine nasal spray were administered as for the previous patient.

After completion of bilateral superior laryngeal nerve blocks, the patient's heart rate slowed to 50 beat min^{-1} and arterial pressure decreased to 60/0 mm Hg. He looked pale and sweaty and became drowsy. He was placed supine and given a total of 0.9 mg of atropine i.v., and normal saline 1 litre was administered quickly. Five minutes later, arterial pressure was 85/50 mg Hg and heart rate 85 beat min^{-1}. He became alert and responsive. When the circulation was stable (after 10 min), local anaesthesia of the upper airway was completed. Arterial pressure before nasotracheal intubation was 100/60 mm Hg and heart rate 90 beat min^{-1}. Tracheal intubation was successful and general anaesthesia and endoscopy were uneventful.

DISCUSSION

Theoretically, superior laryngeal nerve block may cause distortion of laryngeal anatomy. If large volumes of local anaesthetic are used, or the injection is made through the thyroid cartilage, stridor may ensue as a result of oedema of the vocal cords. Vagal stimulation in response to this type of nerve block, although theoretically predictable, has not been reported previously.

A number of causes may have led to this reaction in our patients, including apprehension and subsequent fainting. Digital pressure on a sensitive carotid sinus or excessive manipulation of the larynx during indentification of the hyoid bone may have caused vasovagal syndrome. However, the blocks were easy to perform, and manipulations were gentle and some distance from the carotid sinus. The nerve blocks were carried out by an anaesthetist (S.M.M.) with extensive experience in this field. Furthermore, before operation both patients were well sedated, given anticholinergic drugs and did not react adversely to insertion of an i.v. cannula.

Large doses or inadvertent i.v. administration of local anaesthetic drugs may lead to toxic manifestations, including hypotension and bradycardia. However, accidental i.v. administration was avoided by careful aspiration before injection. Furthermore, at the time of hypotension, patients received only lignocaine 1–2 mg kg^{-1} and none exhibited paraesthesiae or tremors.

In our opinion, in these two patients the bradycardia and hypotension during superior laryngeal nerve block appeared to result from direct neural stimulation of this branch of the vagus nerve by the needle. At this point, the nerve is superficial and easy to locate. If the needle penetrated the nerve or its branches, it is reasonable to suggest this may have led to vagal stimulation. On each occasion, hypotension occurred rapidly while the procedure was being attempted. This nerve block is not usually part of our technique but, in view of the great difficulty anticipated in performing intubation, it was included to enhance the mucosal anaesthesia provided by lignocaine nebulization. We have used this block in awake fibreoptic nasotracheal intubation in a total of 75 patients, but with the exception of these two patients, have not encountered cardiovascular complications.

Excessive oropharyngeal secretions are a problem during fibreoptic intubation, particularly in patients with a compromised airway. Thus an effective antisialagogue premedicant is an essential part of our technique. The use of glycopyrrolate in clinical practice has been compared with that of atropine [3] and the antisialagogue effect has been shown to be approximately five times as potent as that of atropine.

In summary: two patients are presented in whom superior laryngeal nerve block for awake intubation was associated with hypotension and bradycardia. We recommended that patients undergoing this block should receive an adequate dose of an anticholinergic drug, part of which should be given i.v., and an i.v. infusion should be commenced before induction of the block. Patients should also undergo routine monitoring of arterial pressure and electrocardiogram.

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CORRESPONDENCE

JOURNALS FOR POLAND

Sir,—May I appeal through your columns for any back numbers of *British Journal of Anaesthesia* from January 1982 to December 1988. These would be transferred to the University Hospital Krakow in Poland, where it has not been possible to obtain the British anaesthetic journals since January 1982.

Any of your readers who are in a position to help should contact me at the following address:

Department of Anaesthesia,
County Hospital,
Hereford HR1 2ER.

I shall, of course, be happy to arrange transport of any issues.

J. H. W. Ballance
Hereford

AIRWAYS RE-REVISITED

Sir,—"Airways Revisited" [1] implied that transtracheal ventilation is unethical. However, it is a valuable tool with which to guarantee oxygenation in those patients who have very difficult airways [2]. A 13-gauge cannula (Trans Cricothyrotomy Device, VBM) placed through the cricothyroid membrane to provide oxygen provides security for patient and anaesthetist, so that attempts at fibreoptic intubation need not be hurried for fear of desaturation [3]. Puncturing the membrane to inject local anaesthetic is accepted practice—why not inject oxygen?

Blind nasal intubation is conspicuously absent from the editorial. Fibreoptic placement of a tube seems a logical alternative, and both are less hazardous with a cricothyroid needle to provide oxygen or to bypass the problem airway altogether.

Anaesthetists wishing to achieve a great degree of skill at fibreoptic intubation need to practise extensively. This begs the question: is it ethical to try to pass tubes in normal anaesthetized patients, using fibreoptic techniques, without their informed consent?

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Sir—We wish to comment on two aspects of the editorial [1] relating to our article describing a Standard Intubating Position. The first relates to whether or not this position should be regarded as "optimum". It was not our intention to give this impression and we provided no evidence for this view. Our approach to difficult intubation is to determine the requirements for a reproducible definition. While difficulty is often defined in terms of what is seen at laryngoscopy [2, 3], this neglects the important question of technique. For example, if the less experienced fail to achieve the same laryngeal exposure as senior anaesthetists, attention needs to be directed at why this should be so.

The second matter is the reference to tactile tests [4, 5]. Capnographs and fibreoptic bronchoscopes are expensive and, even in well equipped institutions, are not always present. Equipment may fail at a crucial moment, with insufficient time for substitution, therefore clinical tests continue to be useful. After more than 2 years' experience with tactile tests, we are convinced that, in the same way that most anaesthetists regard "seeing is believing" as proof of tracheal intubation, a similar philosophy is appropriate for palpation, although a well-practised technique is important.

We find some difficulty with the implication that infection is a problem with tactile and aspiration tests but not with fibreoptic bronchoscopes or capnographs. Any equipment may become contaminated and careful technique is always appropriate. Details such as attention to sharp teeth and the use of theatre gloves rather than thin plastic gloves are appropriate. It would be unfortunate if the specialty took the view that tactile tests pose too great a risk to anaesthetists while surgeons continue to perform PR and PV examinations. In the latter case the information provided is diagnostic, while in the former it may prove vital.

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Sir,—Thank you for the chance to comment on the letters concerning the editorial "Airways Revisited".

I did not state that transtracheal ventilation is unethical, all I said was that it may be considered so in normal patients. Injection of local anaesthesia does not need the great pressure that oxygen requires delivered through the cricothyroid membrane cannula. I do not use blind nasal intubation and I do not teach the technique as I believe it is no longer necessary. Trauma, bleeding peroperatively and postoperative problems are no longer acceptable to me.

Further, I would not agree with Dr Layman on the matter of informed consent. The technique of tracheal intubation is accomplished by inserting a light source (a laryngoscope). The fibreoptic laryngoscope is merely another method which must be used, albeit after it has been taught correctly.

The comments by Charters and colleagues are accepted for the most part. However, I still believe their investigations remain more academic than practical. If anaesthetists wish to confirm correct tracheal intubation by tactile method, they are free to do so. Certainly, I have not found a great desire to do so by colleagues at home or abroad. Equipment may be sterilized, but infected anaesthetists may not be quite so easy to treat.

R. S. Vaughan
Cardiff

PARAVERTEBRAL BLOCK FOR POST-CHOLECYSTECTOMY PAIN RELIEF

Sir,—Giesecke and colleagues [1] suggested the use of paravertebral block for post-cholecystectomy pain relief, and to diminish the intraoperative response to noxious stimuli. It would be of interest to know the concentration of bupivacaine used, the concentration of adrenaline (if any), and the level at which the blocks were performed in that study.

I have conducted a pilot study in 20 patients undergoing cholecystectomy through a subcostal incision, where paravertebral block using the technique suggested by Eason and Wyatt [2] was used for postoperative pain relief. Twenty millilitre of 0.5% bupivacaine, plain or with adrenaline 1:200000 (in alternate patients) was used at the level of T7. In patients receiving bupivacaine plain the duration of analgesia was 1–3 h and in those in the adrenaline group duration was 3–8 h. There was no pain relief in three patients, which could be attributed to failed technique.

C. M. Kumar
Middlesbrough

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Sir,—In answer to the questions raised by Dr Kumar: the concentration of bupivacaine used for the paravertebral blocks in our study was 0.5%. There was no addition of adrenaline. Bupivacaine 20 ml was injected at T8. Excellent analgesia was attained for a minimum of 6 h in all patients studied.

K. Giesecke
Stockholm

Br. J. Anaesth. (1989), **63**, 130–132

BOOK REVIEWS

Manual of Drug Interactions for Anesthesiology. By R. A. Mueller and D. B. A. Lundberg. Published by Churchill Livingstone, New York. Pp. 336; indexed. Price £19.95.

This new text by an American and a Swedish author is aimed at alerting the anaesthetist to potential interactions between anaesthetic drugs and the patient's concurrent medication. As approximately 25% of surgical patients may be receiving drug therapy on admission, some with drugs not readily familiar to the anaesthetist, the need for such a text exists.

The book is presented in three sections. First, an index of all the drugs described, with chemical and (U.S.) proprietary names. The second section, Philosophy and Theory, gives a brief (18-page) outline of the potential mechanisms for drug interactions and the clinical implications of drug interactions. The final section, the Pharmacology Table, lists the 542 drugs described in detail. They are presented in order of classification in the U.S. formulary, but there are no headings for each classification. Each drug is described briefly under Uses and Mechanism of Action, Side Effects and Interactions with Anaesthetic Agents.

The descriptions are concise, and potential interactions with specific anaesthetic agents are identified. The concise text does, however, raise a problem. In the preface the authors state "When in doubt, if an interaction may be significant (infrequent side effects, largely theoretical interactions, no published reports of interaction in man, etc.), it was mentioned nonetheless". In view of this, it is unfortunate that no references have been included, presumably because of lack of space. This makes it difficult for the clinician to determine the scale of any problem.

This book addresses an important problem in clinical anaesthesia and may make a useful addition to a departmental library.

C. S. Reilly

Anesthesia in Hepatic and Biliary Tract Disease, 1st Edn. By B. R. Brown jr. Published by F. A. Davis Company, Philadelphia. Pp. 300; indexed; illustrated. Price $72.50.

The liver is the largest single organ in the body, and receives 20% of the cardiac output under basal conditions. It is not surprising, therefore, that hepatic function plays a pivotal role in body homeostasis. Dysfunction may arise from different causes, including congenital disease, over-indulgence in drugs including alcohol, hepatitis of various aetiologies, and from invasion by primary or metastatic tumour. In addition, both surgeon and anaesthetist may interfere with function, leading to the development of postoperative jaundice and cellular derangement. If all else fails, liver transplantation now offers an important therapeutic modality in the treatment of the decompensated patient.

In this present volume, Burnell Brown has brought together successfully the physiology and pharmacology of normal liver function with the pathophysiology of these various disease states. In each chapter there is consideration of both altered organ and cellular function *and* the anaesthetic implications of these changes.

Several important contributions could be read with profit by candidates sitting the various professional examinations: hepatotoxicity caused by one or other of the inhalation anaesthetic agents (one of the best and most concise accounts yet published); the management of the patient with extrahepatic biliary obstruction; renal, metabolic and endocrine changes occurring in parenchymatous disease; and the coagulopathies of liver dysfunction. The chapter on postoperative jaundice offers clear guidelines to the investigation of affected patients.

Looking at the first of these chapters in more depth, Brown reviews the problems of hepatotoxicity with the volatile agents, and discusses the limitations of the various animal models beloved of the different groups of investigators. The author comes firmly down off the fence with statements such as "there is no *known* safe interval between halothane exposures" — without attempting to commit himself to injudicious statements over how long is a safe period. The evidence for an immunological basis for halothane hepatitis is cogently presented. The presence of circulating antibodies may be one aspect of the hepatotoxic response, but what does the presence of these antibodies imply in the plasma of a fit individual? Brown quotes one patient with the circulating trifluoroacyl antibodies some 13 years after a halothane anaesthetic. Should this antibody become a routine screening test for all patients undergoing repeat anaesthesia; or are we to condemn a first-rate volatile agent to the archives because of the assumed medico–legal consequences of a rare yet catastrophic reaction? Are the other volatile agents without potential toxic properties? Some of these questions are answered by Brown.

Overall this is a concise, state-of-the-art volume. It has been well prepared, with referencing up to 1987, and the important facts highlighted in table form. There are remarkably few text errors. I would not suggest it is an essential purchase for every anaesthetist, as much of the book offers specialized knowledge on topics the routine anaesthetist will rarely see. Nevertheless, *all* departments would be well advised to obtain a copy for their libraries. At $72.50, it is expensive—but such is the price of excellence.

J. W. Sear

Anaesthesia and the Aged Patient. Edited by H. T. Davenport. Published by Blackwell Scientific Publications. Pp. 328; indexed; illustrated. Price £42.50.

The United Nations Organisation population projections suggest that from 1980 until 2000 the elderly population of the world will increase by 66%, with a range from 95% in Central America to 2.7% in Northern Europe. In developing countries, the least educated classes tend to have more offspring; one reason for this is a desire to have sufficient children to tend their parents in their old age. Improvements in health care are associated with this increased life expectancy. However, a deficiency in health care is the likely reason why the Soviet

Union is the first industrialized nation in peacetime to suffer a significant decrease in male life expectancy: at birth, men may expect to live to only 65 yr, compared with 71 yr in the United States of America.

Although providers of health care are concerned that the consequences of an ageing population are partly demographic, this has more to do with the health expectations of a more affluent and better educated population. The evolution of ageing was explained by Weissman in 1891: it was good for the species because it removed old and worn out individuals from the population, thus limiting overcrowding and promoting further evolution by accelerating turnover of generations. The flaws in this concept are several: the hypothesis presupposes what it sets out to explain; in the wild, animals die normally from predation, disease or starvation; it depends on the advantages to a group rather than to one individual.

Seventeen experts, in addition to the editor, have contributed to this very interesting and well-written book. Its appearance is timely: the Confidential Enquiry into Perioperative Deaths in the United Kingdom published in 1988 pinpointed the lack of senior doctors in decisions to operate on elderly patients, especially seriously ill patients. A chapter on surgical decisions in the aged is therefore most appropriate and is written by a retired general surgeon whom this reviewer remembers, as if yesterday, as a Senior Registrar "on the house". This book presents beautifully and skillfully the problems of the "old" which are relevant to anaesthetists. The words "elderly" refer to patients between 60 and 75 years of age, and "aged" to those older than 75 yr (World Health Organisation).

The book addresses the basic science and demography of ageing, disease patterns in the aged, mechanisms of altered drug effects, fluid and electrolyte balance, and the processes of ageing on the various systems of the body. Particular aspects of preparing for anaesthesia in the aged, types of general and regional anaesthesia are discussed, together with the subjects of postoperative problems, intensive care and chronic pain. How especially true to say, in the context of this book, "... anaesthetists can become more expert at assessment if, by following up their patients, they learn what problems to anticipate". The book concludes with a chapter on the ethics of treatment and research in the aged.

The editor has skillfully made this book intimately relevant to the real world of the anaesthetist. Every department should possess a copy and every anaesthetist should read it.

A. P. Adams

Anaesthesia at the District Hospital, 1st Edn. By M. B. Dobson. Published by World Health Organisation with World Federation of Societies of Anaesthesiologists, Geneva. Pp. 143; indexed; illustrated. Price Swiss Fr. 20.

New books at Christmas time can be a particular delight. I remember the *Rupert Annual* particularly when a child, as the pictures were so good that I didn't have to do too much of the reading to understand the story. In many ways these are the first impressions on receiving *Anaesthesia at the District Hospital* by Mike Dobson. It is a book which is a delight to hold, attractive to dip into and beautifully and clearly illustrated. It is published by the World Health Organisation which is a specialist agency of the United Nations with primary responsibility for international health matters. This is one of three handbooks to be published by WHO for the guidance of doctors providing surgical and anaesthetic services in small district hospitals with limited access to specialist services. The district hospital referred to in the title of this book is not the District General Hospital so well known and understood by U.K. anaesthetists. District Hospitals, in WHO parlance, are primary referral hospitals in outlying areas of developing countries. The handbooks are devised to offer advice to a young doctor with limited experience and limited facilities, but who would be expected to carry out every-day routine procedures in anaesthesia, surgery or obstetrics in such hospitals. Dr Dobson's aim has been to produce a volume which will help these medical officers provide safe and effective anaesthesia. He has succeeded.

The author has struck the right balance between describing an anaesthetic service, suitable techniques and equipment for the developing country without being simplistic or too limited in the clinical practice advised. The style is clear, precise and is easy to read. He has avoided using many complicated medical technical terms and thus this book would be also very helpful a correctly educated and competent non-medical assistant working under supervision in such District Hospitals; however, this is not a manual and has not been designed primarily for these assistants. It is full of extremely valuable information and advice for the inexperienced medical officer.

There are 15 chapters with four appendices and a good index. The chapters vary from Fundamental Techniques through to Anaesthetic Supplies and Equipment and include important subjects such as the care of the unconscious anaesthetized patient, the principles of fluid and electrolyte therapy, preoperative assessment, the conduct of a general anaesthetic, the appropriate techniques available, the apparatus particularly useful for the developing country, in addition to choosing and planning an anaesthetic technique, postoperative care and special problems of paediatrics and obstetrics, together with important medical conditions that every anaesthetist must consider. Each chapter has a number of appropriate illustrations. The illustrations by Derek Atherton and Elizabeta Sacco are to be highly commended; they are an epitomy of clear illustration and augment Dr Dobson's competent text effectively. The method of making an oesophageal stethoscope from a nasal gastric tube and a rubber glove together with a wisp of thread, monitoring ventilation on an EMO, add a certain excitement to the practice of anaesthesia being promoted through this book. The illustrators even seem to have noted that an apparently easy tracheal intubation became a difficult one requiring the use of an introducer shown clearly in one of the figures (fig. 26L & M).

There are one or two interesting omissions. The author has deliberately left out extradural techniques, even though these are more generally understood and perhaps applicable nowadays. The "full stomach" is considered in two sections: one is concerned with awake intubation but does not indicate any local anaesthetic technique that might be helpful; the second, in the section on gastric aspiration, does not mention H_2-receptor blockers. The description of rapid induction sequence for emergency surgery explains the use of pre-oxygenation and cricothyroid pressure and its application by the assistant, but does not give a step-by-step account of this technique.

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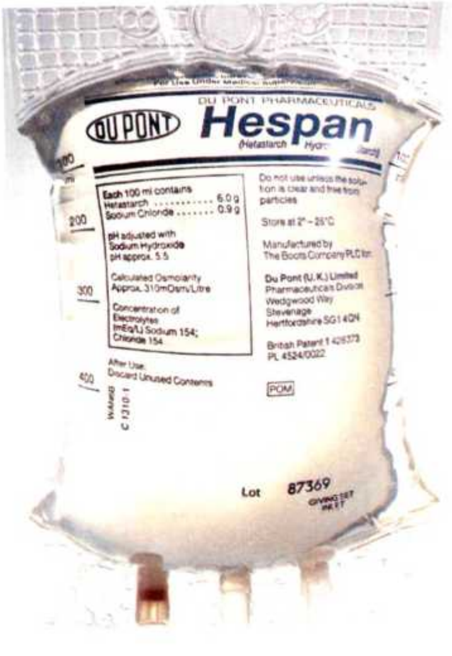
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VOLUME 63, No. 1 *Published monthly* JULY 1989
Annual subscriptions (post free): U.K./Eire £57.00; Abroad £90.00; USA $131.00 (Direct orders only); Trainee rate: U.K./Eire £35.00; Abroad £53.00. Airmail rates on application ISSN 0007–0912

Subscription Department, Professional and Scientific Publications, BMA House, Tavistock Square, London, WC1H 9JR, England

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British Journal of Anaesthesia

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SYMPOSIUM ON ASPECTS OF PAIN

Editor:
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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 63, No. 2 AUGUST 1989

EDITORIAL I

ASPECTS OF PAIN

This issue of the *British Journal of Anaesthesia* is based on the programme of a Scientific Meeting organized by the then Faculty of Anaesthetists, in association with the Journal. On the day before the meeting, a Workshop was arranged at which an invited audience discussed each paper with a view to refining its content before formal presentation and publication. This is the second time that an issue of the Journal has been developed in this way and it is to be hoped that such co-operation will be repeated in the future.

The emphasis of the issue is very much on the management of acute pain, and acute postoperative pain in particular. Our specialty allocates considerable resources to the management of obstetric and chronic pain, but the pain of "routine" surgery has, by comparison, been ignored, although the establishment of a "Task Force on Acute Pain" by the International Association for the Study of Pain is one welcome sign that this is changing. A "distillate" of the implications of the first five papers for the treatment of postoperative pain follows this introduction. The message is clear: we have methods that are more than acceptable; what we must develop is the determination to utilize them effectively, safely and in an appropriate manner. The use of analgesic and sedative drugs in intensive care patients is altogether more complex, but a similar conclusion can be drawn from Aitkenhead's paper on this subject.

The final two contributions are concerned with chronic pain. This is an area of practice where the need for formal allocation of time has long been recognized, although there are still centres where the necessary sessions are not yet available. Anaesthetists have played a major role in establishing the proper management of these difficult patients and it is obvious from Budd's review that it is essential to have a range of skills very different from those needed in the operating theatre. In the final paper, McQuay discusses one aspect of chronic pain management, the use of the opioid drugs, emphasizing how proper procedures for their use will get the best from them.

A number of themes are common to these papers. First, there is good neurophysiological and clinical evidence that, no matter what the cause or type of pain, the earlier that effective treatment is implemented, the better are the results. Second, no one drug or method will provide a solution to the problem of adequate pain management. We must learn a number of methods and select those most appropriate to the patient and his situation. Finally, if an opioid drug is to be used, it seems that the pharmaceutical industry has yet to improve on nature!

J. A. W. Wildsmith

EDITORIAL II

POSTOPERATIVE PAIN—PREVENTION OR RELIEF?

"Slapping the patient on the face and saying: 'It's all over' is a complete inversion of the truth. As far as the patient is concerned, it is just the beginning." [1].

More than 150000 patients a year undergo major abdominal surgery in England and Wales [2]. A few receive effective postoperative analgesia, but there is general agreement among doctors who have taken an interest in postoperative analgesia [3–5] and patients who have undergone major surgery [6–8] that the majority do not.

The first five papers in this issue provide a neurophysiological and clinical basis for the management of postoperative pain. Dr Woolf reminds us that physiological pain—Sherrington's classical noxious stimulus—does not cause tissue damage or an inflammatory response. In contrast, the pathological pain which follows major surgery not only activates the high threshold A delta and C nerve fibres at the site of injury, but also decreases the pain threshold in surrounding, uninjured tissue. In the dorsal horn, a pathological pain stimulus can sensitize and recruit cells which would not respond to a physiological stimulus at the same site, and the resulting central excitability greatly affects the way in which peripheral input is handled by the higher centres. Dr Woolf concludes with two clinically important messages. First, any attempt to obtain total analgesia, which blocks physiological as well as pathological pain, is inappropriate—"the treatment of pain should not simply be the application of techniques that suppress sensation". Analgesia must be more specific than that. For example, local and regional techniques can be very effective in modifying peripheral input, whereas afferent-induced excitability in the dorsal horn is best treated with opioids. Second, prevention is better than relief—"...the dose of morphine required to prevent C fibre induced excitability changes from occurring in the spinal cord is an order of magnitude lower than that required to suppress these changes once they occur". Both these conclusions are supported by clinical experience. McQuay and colleagues [9] showed that opioid premedication, local anaesthetic block and a combination of both increased progressively the time interval from the end of surgery to the first request for analgesia in patients undergoing orthopaedic operations. Morgan, later in this issue, points out that extradural morphine given for the first time on the day after surgery does not produce useful analgesia, but he cites work which suggests that its efficacy might be increased if it is given before the onset of pain.

The papers contain ideas and information which provide a framework for better postoperative analgesia and there will be few readers who do not find some recommendation which will improve the efficacy or the safety of their current practice. Mitchell and Smith make a plea for the routine clinical measurement of acute pain control. They review patient-controlled analgesia (PCA) systems and advocate a continuous background infusion on which the patient may superimpose additional demand boluses. Wildsmith emphasizes that minor as well as major nerve blocks have a significant role and that the type of analgesic method to be used can be matched to the severity of the pain. Morgan sets out the criteria by which spinal and extradural opioids should be judged against conventional methods of analgesia—an area in which anecdotal reports have greatly outnumbered properly controlled trials. He deals in detail with the important subjects of respiratory depression (pointing out that hourly monitoring of the rate of ventilation can be misleading as a measure of respiratory adequacy) and the tabulation of risk factors, such as old age and the concomitant administration of narcotics by other routes.

The reader will also find encouragement for practices which have either become unfashionable or have not yet gained widespread acceptance. Perhaps we can now look forward to the time when opioids once more become the preferred premedicants for major surgery; when the importance of placing extradural drugs at the appropriate dermatomal level is accepted as a *sine qua non*; and when it is recognized that total pain control can be achieved, even after upper abdominal surgery, by combining extradural local anaesthetics with an opioid. Only when total pain control is achieved can we hope to fulfil Kehlet's aim of stress-free surgery producing a decrease in operative morbidity and mortality.

With so much information available, we should be able to plan and implement effective postoperative analgesia. Will our patients benefit? History suggests that they may not. Mitchell and Smith point out that "the available techniques of pain relief have changed little in the past 40 years... despite many advances in the understanding of pain mechanisms". Many patients would add that attitudes towards pain have also changed little. Colin MacInnes, the author, wrote of "the nonchalant attitude of the medical profession towards quite unnecessary suffering—so much so that the one place in the country where you can get least relief is a hospital itself". He considered that the management of postoperative pain was "a cruel and callous disgrace" [8].

Why is it that anaesthetists, who have traditionally been innovative, eager to accept new challenges and ready to move into areas of clinical need, have failed to rise to the challenge of postoperative pain? First, it may be because, given time, postoperative pain disappears, so that if we keep out of the way for the first 48 h, we can avoid the problem at its worst and even deny that it exists. Paradoxically, patients sometimes unwittingly encourage this denial. For every patient who voices dissatisfaction, there are many who say: "Of course, you've got to expect some pain, haven't you, doctor?" Second, we may have retained some atavistic empathy with our predecessors. They, having ensured for their patients several hours of sleep during recovery from deep ether anaesthesia, did not need to concern themselves much with postoperative analgesia, which they were content to leave to the nurses. Certainly, this legacy and the rapid recovery produced by modern anaesthesia are root causes of our present difficulties. One reason for the inadequacy of conventional opioid analgesia is that it is prescribed by members of one profession and administered (or withheld) by members of another, to patients who may be too ill or inhibited to demand it.

How can we ensure that the knowledge and techniques now available are applied so that we can select an effective regimen which is safe and appropriate for the different circumstances in which we work? Two problems have to be overcome. The first is one of organization and logistics. Postoperative analgesia should be the responsibility of a small number of designated individuals. Ready [10] has described the development of an acute postoperative pain management service in Seattle. The service is run by the Department of Anesthesiology and consists of a faculty member, an anaesthesia resident and a clinical nurse specialist. It is unlikely that this system could be widely adopted in this country outside the larger centres, but a team consisting of a Consultant Anaesthetist and two junior doctors, either anaesthetists or house surgeons, can be very effective in a District General Hospital provided that it is Consultant-led and not simply Consultant-based. The second problem is arguably the biggest single barrier to truly effective postoperative analgesia, and it concerns our use of words. We are conditioned to think and talk in terms of "pain relief". Because it is not possible to relieve something unless it has been allowed to occur, our language and thought are misdirected, with the result that we act too late. None of systems of analgesia mentioned in the following papers will yield their full potential unless they are targeted at prevention rather than relief. As well as considerable knowledge of the pharmacological and neurophysiological aspects of pain, we have suitable drugs, equipment and techniques to enable us to control postoperative pain. There are now two immediate needs. First, we should re-assess critically our current practice and, where possible, draw up an improved procedure which is safe and effective in our local circumstances. Second, these changes in organization must be accompanied by changes in thought and terminology so that action is pre-emptive rather than retrospective, and pain prevention* is practised as a routine. It is unlikely that any real progress will be made until we proscribe the use of the term "pain relief" in the context of postoperative analgesia and confine it to areas of practice where we can only respond retrospectively.

E. N. Armitage

**Prevent*: pre-venire. To act in anticipation of, ... to act as if the event or time had already come. (Shorter Oxford English Dictionary.)

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Br. J. Anaesth. (1989), **63**, 139–146

RECENT ADVANCES IN THE PATHOPHYSIOLOGY OF ACUTE PAIN

C. J. WOOLF

The peripheral receptors of the sensory systems have transduction mechanisms that ensure maximal sensitivity to only a small spectrum of the wide range of stimuli that impinge upon them. Because there is a minimal overlap in sensitivity between the receptors of the different sensory systems, each is specialized and possesses its own "specific" or "adequate" stimulus. Maintaining this receptor-generated specificity, sensory pathways in the central nervous system are, to a considerable extent, arranged so that inputs from similar classes of receptor run through neural networks that are closely aligned anatomically. This enables functionally discrete systems such as the visual, auditory and tactile sensory systems to be seen to be structurally distinct. At each level of the neuraxis where sensory information is relayed, complex processing and modulation occurs to assist in defining the location, onset, duration, intensity and dynamic properties of a stimulus. Ultimately, activation of the highest levels of the nervous system may produce a conscious awareness of the stimulus, either as a relatively pure sensation or as a complex hybrid one resulting from parallel sensory inputs. In this way photons falling upon the retina are unambiguously perceived as light, movement of hair cells in the cochlea as sound and deformation of mechanoreceptor terminals in the skin as touch.

Is pain the perceptual consequence of the activation of a specialized sensory system that resembles in its neural organization the visual, auditory or tactile sensory systems? This is not an abstruse academic issue, but the key to understanding the pathophysiology of pain. The current view of many basic scientists and clinicians is that there is a sensory system specific for pain, which has its own receptors, pathways and cortical areas. However, there is evidence that challenges this belief. It suggests that, when pain is viewed from a clinical perspective, it is *not* the inevitable consequence of the activation of a unique pain system but is, instead, an expression of dysfunction in the somatosensory system.

A major reason for the confusion over the nature of pain is that we have all learnt to use the same word, *pain*, to label a wide variety of sensations as soon as they become uncomfortable, unpleasant, irritating, disturbing, severe, intense, distressing, intolerable or disabling. We must resist the temptation of thinking that, because we use a single word to describe these sensations, a single neural mechanism is involved. Pain can instead be divided into two distinct and qualitatively different categories. These are what I have chosen to call physiological pain and pathological pain. The distinction between the two depends on the argument that physiological pain is a "normal" sensation, while pathological pain is the consequence of an "abnormal" state [52].

PHYSIOLOGICAL PAIN

This term is used to define the range of transient sensations we experience in response to stimuli that are of sufficient intensity to threaten to damage tissue or produce small localized areas of injury, but which neither provoke an extensive inflammatory response nor damage the nervous system. Sherrington, at the turn of the century, devised the term "noxious" to describe precisely such stimuli [41]. Physiological pain can be elicited by mechanical, thermal or chemical stimuli and clearly defined thresholds can be established experimentally in trained subjects, at which the sensation stops being one of pressure, hot or cold and becomes painful [21]. The intensity of stimuli that reach the pain threshold is almost identical to that which activates the flexion

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withdrawal reflex [47]. Further increases in the intensity of the stimulus produce a quantifiable stimulus–response relationship until the pain exceeds a certain tolerance level. Although it is possible, using controlled noxious stimuli in trained subjects, to obtain reproducible and quantitative psychophysical data, physiological pain differs from the sensations produced by innocuous stimuli in being particularly susceptible to interference from psychological factors such as anxiety or suggestion and by being accompanied both by autonomic and affective responses.

The reason for calling the sensation elicited by transient non-tissue damaging noxious stimuli "physiological pain" is two-fold. First, in terms of the sensory apparatus involved and the nature of the stimulus–response relationship there are similarities with other physiological sensations. Second, from a teleological perspective, physiological pain has a protective role: because of the unpleasant nature of the sensations involved, we learn to avoid certain stimuli and, because of the simultaneous activation of the flexion withdrawal reflex there is an automatic removal of the body from the source of the stimulus. Physiological pain is something we all experience frequently in our daily lives by touching hot or cold objects or by exposure to intense external mechanical stimuli that may scratch or prick our skin and, indeed, such pain occurs frequently in the clinical context with interventions such as injections.

PATHOLOGICAL PAIN

Pathological pain is that sensation that arises as a consequence of either the inflammatory response that accompanies substantial tissue injury, or damage to the nervous system. Because the natural history, nature and pathophysiology of the pain associated with these two states differs considerably, it is convenient to subdivide pathological pain into inflammatory and neuropathic pain [52]. In spite of their differences, there are important common features in which both types of pain differ from physiological pain. These are:

(1) The pain may occur in the absence of any apparent stimulus.
(2) The response to suprathreshold stimuli may be exaggerated in either amplitude or duration.
(3) The threshold for eliciting pain decreases to a level where what would normally be an innocuous stimulus begins to elicit pain.
(4) The sensation of pain may spread from the site of an injury or a lesion to un-injured or unaffected tissue.
(5) Pathological interactions between the sympathetic and somatosensory systems may occur.

The presence of all or most of these features (spontaneous pain, hyperpathia/hyperalgesia, allodynia, referred pain, sympathetic dystrophy, sympathetically maintained pain) is what makes clinical pain pathological. Pathological pain involves the disruption of the normal selectivity or specialization of the somatosensory system. Instead there is aberrant convergence and the mismatch of stimulus with response. There is no "adequate" stimulus for pathological pain; it may occur in response to the lightest of touches (e.g. in causalgia) or in response to mildly noxious stimuli; the sensation is excessive and more prolonged than would be expected for the nature of the stimulus, and it may even occur in the absence of any apparent stimulation, as after brachial plexus avulsion injury.

THE PATHOPHYSIOLOGY OF PAIN

There is no single pathophysiological mechanism responsible for the production of pain. Physiological pain results from the activation of high threshold receptors in the periphery (nociceptors) which feed in complex ways to a series of ascending pathways that carry information from the spinal cord to the brain. In contrast, inflammatory and neuropathic pain appear to be the consequences of adaptive and maladaptive disturbances which occur within the somatosensory system and can be triggered by a wide variety of different situations. Inflammatory pain retains some teleological resemblance to physiological pain, in that a protective role for the phenomenon can readily be appreciated: tenderness will help to avoid further damage to an injured area while healing takes place. However, neuropathic pain appears to offer no such benefit to the patient and, instead, is the pathological product of a disturbed nervous system.

The differences between the different types of pain are not absolute. In certain circumstances there may be a continuum between them, so that a noxious stimulus which elicits a brief burst of "physiological pain" lasting seconds, may then go on to damage tissue, provoking an inflammatory response setting in train the changes that produce "inflammatory pain" which may last from hours to days. Persistent peripheral tissue injury could, in some situations, lead to either a reactive or a direct modification of the nervous system, thereby inducing chronic "neuropathic pain". What has to be decided is if the neural apparatus that is responsible for physiological pain is identical to that which generates pathological pain. Is physiological pain the result of a transient activation of a specific pain system and clinical pain the consequence of a sustained activation of the same system?

The answer to this key question is both yes and no. Yes, in the sense that elements of the nociceptive neural mechanisms that produce physiological pain are involved in the generation of pathological pain. No, because pathological pain results from *changes* in this and other somatosensory systems, rather than simply from the continued activation of only this system. The nervous system cannot be viewed as a rigid "hardwired" system where certain patterns of input will necessarily produce, in a predetermined fashion, a certain output and all that varies is the amplitude and duration of the signals. Instead, we must recognize that the nervous system is plastic or modifiable and that it is this capacity for change that is responsible to a large extent for the generation of clinical pain states. The plasticity of the nervous system can either be adaptive or maladaptive. Adaptive plasticity underlies the ability of the nervous system to compensate for damage or to produce changes in function appropriate to changes in the environment. Maladaptive plasticity comprises those changes in the nervous system that lead to a disruption of function and, therefore, it may be considered to be a disease state. To a large extent physiological pain is a sensation that reflects certain specific types of peripheral stimuli, while pathological pain is a sensation that is a consequence of changes within the nervous system that result in an alteration in the way in which information from the periphery, some of which may be quite normal, is handled.

There are four categories of change to the nervous system that can result in the pathogenesis of clinical pain:

(1) peripheral sensitization of primary afferents
(2) central sensitization of dorsal horn neurones
(3) abnormal properties in central circuits
(4) permanent changes in the nervous system.

The first three tend to occur during inflammatory pain, while the last three tend to occur during neuropathic pain. There are considerable experimental data on the first two phenomena, less on the third and almost nothing on the fourth. This review will, as a consequence, deal only with peripheral and central sensitization and their contribution to acute pain states.

Peripheral sensitization

Nociceptors, both A delta and C, are characterized by high thresholds and require intense stimuli to activate them [7,26,37]. This property is reflected in the higher intensity of stimuli that are normally required to generate physiological pain, compared with those that elicit innocuous sensations. However, the sensation of pain does not follow the firing pattern of nociceptors in a simple, predictable fashion, and the central processing of the afferent input, in terms of both summation of inputs and inhibitory interactions, is extremely important [1,21,35,37].

After peripheral tissue injury the threshold for eliciting pain decreases both within the area of the injury (primary hyperalgesia) and in the surrounding uninjured tissue (secondary hyperalgesia) [8,37,44]. In the zone of the injury, the increased responsiveness is to thermal and mechanical stimuli, whereas in the surrounding zone the sensitivity is exclusively to mechanical stimuli [8]. Contributing to the primary response to heat are changes in the sensitivity of the thermal nociceptors [36]. These include a decrease in threshold, an augmented response to suprathreshold stimuli and spontaneous activity. Similar changes have not so far been found for the mechanonociceptors, even though mechanical hyperalgesia is a prominent feature of tissue injury in man and animals [37,51]. This means either that the afferents that change after tissue injury have not been found yet, the assumption being that there may be a population of totally insensitive afferents that will not be detected unless their receptive field area is injured, or that the peripheral injury induces alterations in the way that the CNS responds to normal stimuli (see section on central sensitization).

The precise molecular mechanisms responsible for the alteration in the sensitivity of a nociceptor after tissue injury are not known. Many of the biochemicals released directly or indirectly by damaged tissue (bradykinin, histamine, substance P, the leukotrienes, prostaglandins and other arachidonic acid metabolites) have the capacity either to excite nociceptors or to increase their sensitivity [3,22,37]. Although a role for mast cells in these changes has been recognized, there is recent evidence suggesting that the terminals of post-ganglionic sympathetic efferents are also involved, possibly by the release of a neuropeptide or of ATP [23]. The chemosensitivity of nociceptors may be both a part of the way in which they detect a change in their local environment (e.g. damaged tissue) and the means by which their sensitivity to non-chemical stimuli is altered. If an inflammatory mediator binds to a receptor on an afferent terminal and induces a change in the level of a second messenger in the terminal, this could (without necessarily involving any action potential discharge) result in an alteration in the afferent's sensitivity by the phosphorylation of a membrane-bound receptor [38].

The spread of the sensitization of primary afferents by the axon reflex is the mechanism which Lewis originally suggested could explain the generation of secondary hyperalgesia in uninjured tissue [24]. Although the antidromic activation of C fibre afferents does occur and contributes to the neurogenic inflammatory response, when peripheral changes in sensitivity in the zone of secondary hyperalgesia are detected [14] they are too small to account for all the injury-induced alterations in either behaviour or sensibility [36]. Consequently we are forced to look centrally for an alternative process which, by acting in concert with peripheral sensitization, can produce the full picture of clinical pain [49, 51].

Central sensitization

The peripheral terminals of primary afferent neurones are specialized to encode particular features of the stimuli that impinge upon the body surface. Centrally, this specialization is maintained by the order in the spatial location and morphology of the central terminals of the afferents [5,54]. The dorsoventral distribution of the central terminal arbors in the dorsal horn of the spinal cord reflects their modality responsiveness and threshold [5,25,42], while their mediolateral and rostrocaudal position is related to the location of their peripheral receptive fields [43]. This somatotopically organized afferent terminal map provides a structural framework for the transfer of the electrical activity generated by cutaneous stimuli to dorsal horn neurones.

The cutaneous receptive fields of dorsal horn neurones, while somatotopically organized [2, 6,9,55,56], do not have the same degree of high spatial order that primary afferents have. Assessment and classification of the cutaneous receptive fields of neurones in the dorsal horn have, however, largely been based on the assumption that the receptive field properties of these neurones are fixed and unchangeable. Nevertheless, spontaneous variation in receptive field properties has been observed [12] in response to descending influences [28], pharmacological agents [39,65] and as a result of nociceptive afferent input [11,13,15,40,57,60]. One of the first indications that afferent input could alter the response properties of spinal neurones for prolonged periods emerged from studies on flexor alpha motoneurones. These neurones are characterized by absent spontaneous activity and discrete high threshold cutaneous receptive fields, stimulation within which evokes a phasic discharge of the motoneurones [10,59]. Peripheral tissue injury results in the development of a background discharge in the motoneurones, a decrease in the threshold of their receptive fields and a change in the pattern of the reflex from phasic to tonic [49,50,58]. These hypersensitivity changes, which resemble pain producing hypersensitivity states after injury in man [37,52], can be duplicated by brief (20-s), low frequency (1-Hz) trains of electrical stimuli to peripheral nerves, provided that the stimulus intensity is sufficient to activate C fibre afferents [46,61]. Different C fibre afferents have, moreover, different central effects, depending on the tissue that they innervate, muscle afferents having more prolonged actions than cutaneous ones [46]. The size of the cutaneous receptive fields of the flexor motoneurones expands after peripheral injury or brief C fibre afferent conditioning stimuli, including in many cases the recruitment of novel contralateral inputs [49].

Brief afferent conditioning stimuli have more recently been shown to induce prolonged changes in the receptive field properties of dorsal horn neurones, including a population that projects to the brain [11]. These changes, which have a time course similar to that of the facilitation of the flexion reflex, include both expansions in the size of receptive fields and a change in the types of stimuli that activate these cells. These changes indicate that a static classification of the receptive field of a neurone does not take into account its potential response repertoire. A "nociceptive-specific" neurone in one context may, for example, begin to respond to low threshold afferent fibres in another.

Intracellular studies of dorsal horn neurones *in vivo* reveal the way in which receptive plasticity occurs by demonstrating that, in addition to an impulse firing zone (that area of skin where stimulation generates a discharge of action potentials), the receptive fields of many dorsal horn neurones also contain a subliminal zone (that area of skin where the stimulus only produces subliminal or subthreshold responses). The subliminal responses of dorsal horn neurones represent a reservoir of functional activity that is potentially available, if either the amplitude of the subthreshold inputs or the excitability of the cells, increases [57, 60]. Under normal circumstances the postsynaptic potentials generated by primary afferents are too brief to produce anything other than a few hundred milliseconds of perturbation of excitability and this, together with segmental and descending tonic and phasic inhibitory mechanisms, acts to stabilize receptive fields. However, when peripheral injury activates high threshold afferents, they trigger alterations in the spinal cord—the phenomenon of central sensitization—that recruit the subliminal components of the receptive fields to a level where they become suprathreshold, and these changes alter the way in which peripheral input is handled by the spinal cord and, therefore, by the higher centres to which the information is ultimately transferred [57].

How do C afferent fibres produce long lasting changes in the dorsal horn? The most satisfactory explanation at present is that these afferents have at least three different actions on dorsal horn neurones:

(1) They produce a fast transmitter-mediated excitatory input to those cells with which the C fibres make a direct monosynaptic contact [17, 18]. In this way they transfer information relating to the location, onset, duration and intensity of high intensity peripheral stimuli.

(2) As a result of the release of neuromodulators (co-released from the same terminal as the fast transmitters) they produce a slow excitatory potential [20, 64], giving the afferents the capacity to produce progressive response increments when stimulated repeatedly [31] (wind-up). Thus the identical stimulus evokes successively larger and larger responses as a result of summation of the slow potentials [20].

(3) Brief C fibre inputs can produce prolonged alterations in receptive field properties which outlast the periods of both the stimulus and the depolarization, and therefore are not directly linked to a sustained synaptic input [11, 57].

The fast excitatory transmitter is likely to be an amino acid such as glutamate which, by acting on quisqualate/kainate or other similar receptors, will produce a short duration inward current, generating a fast monosynaptic excitatory postsynaptic potential lasting approximately 10 ms [17, 19]. Simultaneous release of peptides such as substance P or calcitonin gene related peptide [63], which are contained within the same afferent terminal [4], produces further inward currents [32], but with a longer latency and a longer duration as a result of acting on calcium and sodium channels and by decreasing outward potassium current [33, 34, 45]. Slow potentials produced by small calibre afferents last for tens of seconds and provide the opportunity for considerable temporal summation [20]. Such temporal summation has been shown in human volunteers to be important in the build up of pain that occurs when noxious stimuli are repeated at low frequencies [35].

How can these postsynaptic actions of small calibre afferents which last from milliseconds to seconds produce changes that last for hours? The key to this is a change in intracellular calcium or other second messengers produced during the course of the slow potential. The depolarization may itself increase calcium entry into the cell by opening voltage-dependent calcium channels [27, 48] or by decreasing magnesium blockade of NMDA receptors [30]. Alternatively, the changes in second messengers may be independent of depolarization and instead be produced by a receptor-mediated increase in calcium, cyclic AMP, cyclic GMP, IP3, *etc.* Second messenger systems can, by acting through protein kinases, modify excitability for prolonged periods by phosphorylating ion channels or membrane-bound receptors. Alternatively, they may produce even longer lasting changes by altering gene expression [16, 53].

Such a series of events shows how a noxious stimulus, by activating C fibre afferents, can change the excitability of dorsal horn neurones and alter their receptive field properties. Alterations in sensory processing in the dorsal horn will ultimately be reflected as altered perception of peripheral stimuli, including feeling pain in response to innocuous ones. What we feel then is not necessarily an accurate indication of the nature of the stimulus. The alteration in the excitability of dorsal horn neurones also alters the activity generated in preganglionic sympathetic motoneurones. Sympathetic reflexes will be exaggerated and prolonged in much the same way as flexion reflexes. This has important peripheral consequences, because of the interactions between the terminals of postganglionic sympathetic efferents and the terminals of primary sensory neurones [23]. Sympathetic activity has the capacity to drive injured afferents, which develop an increased sensitivity to alpha-adrenergic stimulation. In this way a positive feed forward circuit is established in which afferent input initially generates central sensitization, which increases sympathetic outflow, which further increases afferent input, *etc.* [52].

CONCLUSIONS

Three important predictions related to the treatment of pain can be made on the basis of recent information on the pathogenesis of clinical pain. The first of these is that the adequate management of such pain will require techniques that are aimed at the changes that can occur in the central nervous system, instead of only interrupting the flow of sensory signals. In other words, the aim should not be to produce total analgesia, which blocks physiological as well as pathological pain, but to depress or reverse afferent-induced excitability changes in central neurones. The opioids are a good example of drugs which at appropriate doses can do precisely this. In order to design drugs or techniques that are able to reverse this modification of the central nervous system, it is clearly vital that we understand precisely what these changes are at cellular level.

The second prediction is in many respects a corollary of the first, and it is simply that the most effective way of treating clinical pain is to design management procedures that prevent the occurrence of plasticity in the nervous system. There is experimental evidence that the dose of morphine required to prevent C fibre induced excitability changes from occurring in the spinal cord is an order of magnitude lower than that required to suppress these changes once they occur [62]. Recent clinical trials have confirmed this by showing that postoperative pain is decreased if the patient has either a local anaesthetic block, such as an extradural, or is given morphine before the surgical intervention [29].

Any surgical procedure that generates a barrage in the small calibre afferents will, in a lightly anaesthetized patient, produce changes in the central nervous system that will subsequently lead to the amplification and prolongation of postoperative pain. Ideally, treatment of pain should begin before it is required. Using the same rationale, it may also be possible therapeutically to decrease some of the chronic problems that follow deafferentation (i.e. phantom limb pain) by modifying the afferent signals that may contribute to maladaptive plasticity.

The third prediction is that treatment of established pain will be most effective when attempts at returning a disordered nervous system to normal are directed not only at trying to break the afferent limb that sets up the changes in the nervous system, but also at acting on the sympathetic disturbances that perpetuate the disorder. Strategies for treatment must recognize and aim to eliminate both those factors that are responsible for initiating the vicious circle of maladaptive plasticity and those which perpetuate it.

The treatment of pain should not simply be the application of techniques that suppress sensation. We need to understand the natural history of the different pain states in order to interrupt their development. This understanding will only arise from an intensive analysis of somatosensation at a basic science level. The questions that need to be asked, though, should be directed by clinical observation. Clinicians dealing with pain need, in turn, to recognize that the nervous system reacts dynamically both to the situations that produce the pain in their patients and to their clinical interventions, some of which may exacerbate rather than reduce pain.

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Br. J. Anaesth. (1989), **63**, 147–158

THE CONTROL OF ACUTE POSTOPERATIVE PAIN

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In recent years, the special knowledge and abilities of anaesthetists have extended into the fields of chronic pain control and the control of pain in labour. However, acute pain, and particularly the treatment of postoperative pain, has received less attention. Although there is now a surge of interest in acute pain [29], the majority of patients undergoing major surgery still receive techniques of pain relief that have changed little in the past 40 years. This situation pertains despite many advances in the understanding of pain mechanisms, the action of analgesic drugs and the development of sophisticated systems for drug delivery. This review examines recent work on the pharmacology of the analgesic drugs and systems for their delivery, and considers their systemic use in the control of acute, especially postoperative, pain.

Definition of acute pain

There is no clearly defined distinction between acute and chronic pain. In general, acute pain is associated with a distinct disease or injury and it is assumed that the time-course of the pain is limited to the period of repair of the injury. However, some acute pain states may progress to become chronic. This may result from progression of the disease process or from a disturbance in neurophysiology following repair of the original injury.

Acute pain is an extremely complex sensation which extends beyond simple nociceptor input, the central processing of which is modulated strongly by emotive elements such as fear, anxiety or depression and by previous experience of pain. It is difficult to quantify the contribution of these elements in the overall experience of acute pain observed in an individual patient. Although it is easier to regard acute pain as a single sensation, some regard must be paid to the contribution of each factor, despite the difficulty of assessment, because it may influence rational treatment. This can be extremely difficult in practice and may require complex multi-dimensional scoring techniques which are not often appropriate to acute pain and are frequently confined to the treatment of chronic pain.

PSYCHOLOGICAL ASPECTS OF ACUTE PAIN

There are enormous individual variations in patient response to acute pain and this variability is well recognized after surgery. Many clinicians have encountered the occasional patient who requires little or no analgesia even after major surgery, but they recognize that, at the other extreme, there are those for whom it seems impossible to provide adequate analgesia, despite the best efforts of the attendants. These extremes presumably lie at the opposite ends of a distribution curve for susceptibility to pain and it is widely held that psychological variables account for many of the observed differences. As noted above, pain is a complex summation of nociceptive input, emotion, state of arousal, thought processes and social influences. Psychological approaches may be utilized not only to assess the susceptibility of an individual to acute pain, but also as part of rational therapy [9].

Situational stress

The simple event of hospital admission produces a significant stress response. The individual's response to the strange environment has been shown to correlate closely with subsequent pain perception. Four particular factors were associated: loss of independence, spouse separation, isolation and lack of information.

Pre-existing psychological stress

Three major variables influence the degree of distress of patients undergoing surgery.

Anxiety–Tranquillity. The subjective state of

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anxiety can be sub-divided in different ways. "Anticipatory" anxiety is that evident before a forthcoming unpleasant event and "concomitant" anxiety is that associated with the event. Recent work [36] suggests that the two are linearly related, that is, patients who are anxious before surgery are more distressed afterwards. "State" anxiety is that associated with a certain set of circumstances and "trait" anxiety is applied to those who tend to react with strong emotion to any stressful experience. Scott, Clum and Peoples [36] have shown that preoperative state anxiety has a linear relationship with postoperative pain.

Some patients use the defence mechanism of denial as a means of removing the unpleasant feeling of anticipatory anxiety. In doing so, they refuse to think of possible future events of which they are afraid. Thus, although they may have very low anticipatory anxiety scores, they will vary greatly in their concomitant anxiety when confronted with pain. Some may be able to maintain the process of denial throughout, while others may suffer great distress as the stimulus overwhelms the denial mechanism. This obviously depends on the severity of the stimulus and the "coping" abilities of the patient.

Helplessness–active control. Helplessness is well recognized as a major cause of stress. Patients in acutely painful situations often feel powerless to exercise any control over their state. Thompson [42] has identified four components to this:
(1) Behavioural control. This describes any manoeuvre which the patient can use to decrease the perception of pain; for example, relaxation or breathing exercises or the provision of a patient-controlled analgesia device.
(2) Cognitive control. This comprises the alteration of pain by thought processes. These can act both to reinforce the pain (e.g. by concentration on or re-interpretation of the pain) or decrease the pain (e.g. by denial, dissociation and distraction).
(3) Information. Provision of adequate information reduces the uncertainty, and therefore the distress, of a painful experience. Films or videotapes may be useful, particularly in paediatric practice, in familiarizing the patient with an unaccustomed experience.
(4) Retrospection. The re-interpretation of a past painful event may alter the current implications of that event. This obviously has less bearing on the management of current acute pain.

Positive and negative feelings. When the patient anticipates great benefit from the proposed operation, he may be more willing to trade short-term discomfort for long-term gain. Where the surgery involves mutilation, confirmation of a poor prognosis or no perceived gain in the patient's mind, the additional anxiety may compound the difficulty of providing postoperative analgesia.

ASSESSMENT OF ACUTE PAIN

Therapeutic manoeuvres in medicine should be monitored by assessment of effect. It is an indictment of the current practice of acute pain control that some measure of the adequacy of the analgesia provided is not obtained routinely. Instead, reliance is placed on subjective assessment by nursing attendants, who have little power to modify an inadequate prescription which is provided by the physician on a "safe guess" basis. Research in pain control has yielded many, often complex, assessment systems. While these are likely to remain largely within the province of the research worker, there is a strong case to be made for applying some of the simpler techniques in everyday clinical practice.

Objective methods of scoring pain have relied upon assessment of biochemical indices such as changes in plasma concentrations of hormones, but these tend to be inaccurate, expensive and not applicable in clinical practice. However, measurement of respiratory function, particularly FEV_1 and PEFR, is useful in patients who have undergone thoracic or upper abdominal surgery [8]. Although an experienced observer may be able to make a coarse assessment of the degree of pain suffered by a patient, it is accepted widely that the amount of suffering may only truly be assessed by the individual concerned.

Unidimensional scales

With unidimensional scales, the patient is asked simply to define the severity of the pain itself. In its simplest form, the patient may be asked whether or not he feels pain, without any measure of degree. The lack of sensitivity here is obvious. In many acutely painful situations, a total lack of pain is not an obtainable endpoint. Some description of intensity is therefore necessary. A simple verbal rating scale (VRS), such as "none", "mild", "moderate" and "severe" has been shown to have the best correlation with visual analogue scales (*vide infra*) and an acceptable degree of variation between individuals. Numerical rating scales allow a greater degree of sensitivity. It is believed that they circumvent one of the problems of visual analogue scores, which some find confusing because of the wide freedom of choice presented.

Visual analogue scales (VAS) have now been used widely as a sensitive and valid measure of pain intensity. The common pattern is to use a line 10 cm long with extremes labelled "no pain" and "worst pain imaginable". However, some patients find them confusing and they do require a certain degree of wakefulness and co-ordination to complete. These disadvantages can be circumvented partly by the use of slide-rule devices, which may be processed electronically. VAS may be more efficient for charting the progress of an individual patient rather than for inter-individual assessment. Pain intensity difference (PID) is the difference in pain score at a time after the administration of a drug compared with the pain score at time 0—before any analgesic was given. Summed pain intensity difference (SPID), the sum of PID over a certain period, gives a useful measure of relative efficacies of treatment over the study period, between different patients or groups.

Multi-dimensional scales

The Magill Pain Questionnaire is a well-established tool which assesses pain under three dimensions: sensory, affective and evaluative. While useful in research and in chronic pain states, it is too cumbersome for repeated evaluations of acute pain states in clinical practice. A simpler method of introducing further dimensions into acute pain scoring is to use VAS ratings for anxiety–tranquillity in addition to no pain–severe pain.

We suggest that, where possible, all patients in acute pain should have an assessment of the adequacy of analgesia. This should be as normal as recording of heart rate and arterial pressure. A simple unidimensional scale (VRS or VAS) would be better than no score at all and would provide the degree of feedback that is lacking in present-day practice.

PHARMACOLOGICAL CONSIDERATIONS IN ACUTE PAIN

The burgeoning of knowledge in the neurophysiology and pharmacology of pain in recent years has been spectacular, although this knowledge has yet to have a major impact on the treatment of acute pain for the majority of sufferers.

Pharmacology of the Opioid Drugs

There have been great advances in two areas in recent years: the understanding of opioid receptors and the development of new drugs acting on these receptors.

Opioid receptor theory

For a fuller description of this topic the reader is referred to excellent reviews by Jordan [18] and Yaksh [46].

In common with other neurotransmitter/hormone systems, it is now known that the opioid system comprises several distinct receptor subgroups and a wide range of endogenous ligands. The physiological significance of the endogenous opioid peptides is not yet fully established, but it is possible that, in the future, synthetic analogues of these substances may be produced and used in the practical management of pain.

The original work of Martin [21] proposed three receptor types: mu, kappa and sigma. Further work in animals has suggested the existence of two other receptors, delta and epsilon, and possibly many others, the significance of which is unclear at present. Table I describes the three main receptor subtypes. Drugs may act as agonists, partial agonists or antagonists at any or all of these receptors. Thus the simplistic description of some of the newer synthetic opioids as

TABLE I. *Characteristics of the three main types of opioid receptor*

	Receptor		
	mu	kappa	sigma
Analgesia	Yes	Yes	No
Respiration	Depression	Depression	Stimulation
Behaviour	Euphoria	Sedation	Dysphoria
Pupil	Miosis	Miosis	Mydriasis
Morphine withdrawal	Suppression	No suppression	No suppression

TABLE II. *Effects of seven agents on the three main types of opioid receptor. NA = No activity; PA = partial agonist. (Adapted from Rosow [31])*

	Receptor		
	mu	kappa	sigma
Morphine	Agonist	Agonist	NA
Buprenorphine	PA	NA	NA
Meptazinol	PA	NA	NA
Nalorphine	Antagonist	PA	Agonist
Pentazocine	Antagonist	PA	Agonist
Nalbuphine	Antagonist	PA	Agonist
Naloxone	Antagonist	Antagonist	Antagonist

"partial agonists" tends to obscure their true action. Table II illustrates a proposed receptor interaction scheme for some currently available agents.

Pure agonist drugs

Despite the current availability of several new agonist/antagonist or partial agonist drugs, the pure agonists remain the mainstay of the treatment of acute pain. Morphine is the "gold standard" against which any new drug must be compared.

All opioid agonists produce analgesia, respiratory depression, euphoria, decreased gut motility, nausea and cough suppression, and have the potential to cause urinary retention. In the doses used in normal clinical practice, they produce analgesia without marked depression of consciousness. Unlike most of the agonist/antagonist drugs, however, there is no "ceiling effect" to their analgesia and respiratory depression and very large doses have been used as a sole agent in cardiac anaesthesia; even with these enormous doses, loss of consciousness is not always assured.

Differences between agents result largely from differences in pharmacokinetic profiles or from effects on non-opioid systems, rather than distinct pharmacodynamic effects. For example, the onset time for analgesia with morphine is slower than that with fentanyl because the former has a lower lipid solubility, and the ability to cause histamine release possessed by morphine is absent with fentanyl.

It is well known that there are great variations in plasma opioid concentration profiles after i.m. administration: for example, it has been demonstrated with pethidine that there is a 2–5 fold difference in peak plasma concentrations and a 3–7 fold difference in the rate at which these concentrations are achieved after a single i.m. injection [4]. Thus the pharmacokinetic properties quoted usually for these drugs are those calculated after i.v. injection. Figures for the agents used commonly are shown in table III. These data do not have much bearing on the latency or duration of action of an i.v. dose of the drug—properties which are governed by the lipid solubility and partition characteristics in blood.

All opioids are weak bases and at physiological pH they exist in both ionized and un-ionized forms. Only the unbound and un-ionized form (which is relatively lipid soluble) is free to penetrate lipid membranes, gaining access to the site of action or biophase. This proportion is termed the diffusible fraction and amounts to 16% of plasma morphine, 2.5% of pethidine and 1.4% of fentanyl. However, as stated, the actual lipid solubility of the drugs varies greatly. The octanol:water partition coefficient for morphine (free base) is 6, for pethidine it is 525 and for fentanyl 11220. The product of diffusible fraction and lipid solubility gives the "diffusing potential" into the CNS. Taking morphine to equal 1, the relative ratios for pethidine and fentanyl are 13.6 and 162, respectively [17].

Variations in patient characteristics may lead to wide variations in pharmacokinetic parameters. In hepatic disease, it has been shown that the beta half-life of pethidine is approximately doubled because of decreased drug clearance. The oral bioavailability of pethidine is increased greatly in patients with hepatic cirrhosis, although there is little change with morphine or fentanyl [5].

The extremes of age have a marked effect. In neonates, the terminal half-life of pethidine is several times longer than in an adult. In patients older than 80 yr, the clearance of pethidine is decreased and the volume of distribution is smaller. The beta half-life of fentanyl is twice as long in elderly patients and this has been attributed to decreased drug clearance [5]. Impaired hepatic metabolism or decreases in liver blood flow may be factors in this observation.

Other drugs may affect the pharmacokinetics of opioids. Enzyme inducing agents such as phenytoin or phenobarbitone decrease the terminal half-life of pethidine. By inhibiting hepatic microsomal enzymes involved in oxidative processes, cimetidine impairs the metabolism of both pethidine and fentanyl. As morphine is metabolized predominantly by glucuronidation, its clearance is not affected.

TABLE III. *Pharmacokinetic properties of some opioid drugs*

	Morphine	Pethidine	Fentanyl	Alfentanil	Buprenorphine
Initial volume of distribution (litre)	23	88	60	11	14
Total volume of distribution (litre)	224	305	335	27	188
Initial half-life (min)	1.7	7.1	4.1	8	2
Terminal half-life (min)	177	222	185	98	184
Clearance (ml min^{-1})	1050	1020	1530	238	1275

It is now well-recognized that the metabolites of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), are biologically active [13]. A recent study of patients receiving long-term oral morphine medication showed an analgesic ratio of morphine to M6G of 1:10 [27], whereas an earlier study had shown a ratio of 1:2.5 after a single dose [35]. This may partly explain the higher analgesic efficacy of repeated doses compared with single doses, at least in chronic pain. In end-stage renal failure it is known that the terminal half-life for morphine is the same as in normal subjects [1]. Recently, it has been shown that the prolonged duration of action of morphine in these patients may be a result of relative accumulation of M6G [37].

Opioid agonist/antagonists

With pure agonist drugs, increasing the dose generally causes an increase in analgesia and in respiratory depression. Thus the maximum analgesic effect obtainable is extremely high and is obtained with doses well outside those that can be used in clinical practice with spontaneously breathing patients.

Measurement of efficacy is extremely difficult with regard to the agonist/antagonist opioids, largely because dose–response relationships for these drugs are not linear. Indeed, depending on the relative affinities of the drugs in their agonistic and antagonistic effects, the dose–response curve may be U-shaped or bell-shaped. All the available opioid drugs in this class demonstrate a bell-shaped curve in animal studies. This implies a high affinity for the agonistic effect and a low affinity for the antagonistic effect; thus in low drug concentrations the agonistic effect predominates, but in higher concentrations antagonism predominates. If the transition between agonism and antagonism occurs within the clinical dose range, the drug has low efficacy at higher doses for severe pain. This phenomenon has been demonstrated in patients treated with nalbuphine after upper abdominal surgery [28].

The unusual dose–response relationships of these drugs also introduce difficulty in assessing equipotency. Given that the drug under study has a sufficiently high "ceiling" (i.e. that the degree of pain anticipated is not close to the plateau of efficacy of that drug), the standard models of postoperative pain may be used to establish equipotency with a standard agent, for example morphine, in a certain dose. However, because there is no certainty that the log dose–response relationship of the agent studied is linear, statements on equipotency with morphine can be made only in relation to the dose used [19].

Pentazocine. This drug was the first agonist/antagonist to become established in clinical practice. It is presumed to be an agonist at kappa and sigma receptors and an antagonist at mu receptors. Doses of 30–50 mg produce analgesia and respiratory depression to an extent approximately equivalent to that obtained with morphine 10 mg; increasing the dose above this intensifies side effects, but does not increase analgesia. Pentazocine causes an increase in heart rate, pulmonary arterial pressure and cardiac work [2] and is therefore best avoided after myocardial infarction.

The usefulness of pentazocine is limited by the high incidence of dysphoria, hallucinations and bad dreams associated with its administration. The technique of "sequential analgesia" [30], in which pentazocine was used at the end of surgery to antagonize large doses of fentanyl given during operation has not found widespread acceptance.

Nalbuphine. This agent was introduced to the U.K. relatively recently, but has been available in the U.S.A. for many years. It appears to act as a kappa and sigma agonist and has quite potent mu antagonist properties. Although it is thought to be approximately equipotent with morphine, several studies have shown that it has a low ceiling effect. If adequate analgesia is not obtained with a low dose, waning of analgesia occurs with increasing dosage, although it then causes marked depression of conscious level [28]. Therefore the agent is not recommended for the treatment of severe pain such as follows upper abdominal surgery [12]. It does not possess the deleterious haemodynamic effects of pentazocine when used for the pain of myocardial infarction.

Buprenorphine. This agent is thought to act as a partial mu agonist. It appears to have limited efficacy, but an extremely high affinity for the receptor. It has a very high lipid solubility, but its speed of onset is limited by a low diffusible fraction and a rapid decrease in plasma concentration (because of a large total volume of distribution) after a single i.v. dose. Its duration of action is prolonged (5–6 h after i.m. injection). Its potency is approximately 25–50 times that of morphine. High lipid solubility lends this agent a useful property: that of excellent absorption by the sublingual route. If buprenorphine is swallowed, extensive first-pass hepatic metabolism results in a low bioavailability and therefore little danger of overdosage if a patient accidentally swallows the tablet(s). A ceiling effect for respiratory depression has been demonstrated with this agent in animals, but significant respiratory depression may occur with the doses used clinically. The effects of buprenorphine are not antagonized readily by naloxone. Doxapram, a respiratory stimulant, is recommended if significant depression of respiration occurs.

Buprenorphine is relatively devoid of side effects such as dysphoria and hallucinations and causes subjective effects similar to those of morphine. In controlled trials in acute severe pain, the incidence of nausea and vomiting was not significantly greater than that observed with morphine. The often-reported clinical observation that nausea and vomiting are major problems with this agent may simply be a reflection of its widespread use in less severe pain. Because of its extremely high affinity for the mu receptor, there is a theoretical possibility that the effects of pure agonist drugs given during anaesthesia may be attenuated in a patient receiving this drug before operation. Indeed, buprenorphine has been suggested for use in a modern resurrection of the technique of "sequential analgesia" (*vide supra*).

Buprenorphine is probably the most useful agent among the recently-introduced agonist/antagonists. It is the only one currently available which has been found consistently of value in acute, severe pain.

Meptazinol. This agent is unusual in that, in addition to partial agonistic effects at the mu receptor, it appears to act by other mechanisms. The role of these other mechanisms, which are thought to be mediated through cholinergic systems, is not clear in man. It has been shown to be effective in postoperative pain [38] by parenteral administration and has a potency approximately similar to that of pethidine. It is well absorbed rectally, but it has been shown that a dose of 150 mg by this route is not adequate for treatment of pain on the first day following hysterectomy [23]. It is said to have a low potential for respiratory depression and its effects can be reversed with naloxone. However, recent work (Hanning and colleagues, in preparation) has shown that the frequency of episodes of arterial desaturation in elderly patients after hip replacement was similar in patients receiving either meptazinol or morphine by patient-controlled analgesia. Side effects (nausea and vomiting) have been reported to be troublesome in obstetric analgesia and it does cause sedation. However, it causes a low incidence of dysphoria and hallucinations, presumably because of lack of action at the sigma receptor.

Non-Steroidal Anti-Inflammatory Drugs in Acute Pain

There is a bewildering number of non-steroidal anti-inflammatory drugs (NSAID) currently available. Although their major use is in chronic pain, there is an increasing interest in their use as adjunctive therapy for acute pain states. The rationale for this is that soft-tissue inflammation may be a potent factor in postoperative pain. However, most of these agents require oral administration and are not usually appropriate for severe acute pain, although some are available as suppositories. While Martens [20] showed that rectal naproxen greatly decreased the requirement for opioids after orthopaedic surgery, work in our department (in preparation) has shown that suppositories containing diclofenac 150 mg had no morphine-sparing effect after cholecystectomy. However, this agent has been found effective for post-tonsillectomy pain in children [44]. Ibuprofen by suppository has been found to produce a 20% decrease in morphine requirements after lower abdominal surgery [24].

Diclofenac is noteworthy in this group for being currently available in an injectable form (for i.m. use only). This has been shown to be of value in acute renal colic, and has been found to be as effective as i.m. papaveretum after hip surgery [7]. A study in patients after abdominal surgery [15] showed a significant morphine-sparing effect, although the study may be criticized for failing to standardize between upper and lower abdominal surgery.

It seems likely that NSAID will prove more effective for analgesia after orthopaedic surgery than after abdominal surgery. The question of whether or not the well recognized side effects of these drugs (inhibition of platelet function and gastrointestinal irritation) represent significant problems in the management of acute pain can only be answered by large scale studies.

POSTOPERATIVE PAIN

This is obviously the area of acute pain control of most interest to anaesthetists. It comprises the largest group of patients suffering acute pain and management has long been recognized as suboptimal. Its transitory nature, however, should render it more amenable to treatment than chronic pain [39].

Conventional Therapy

Treatment has traditionally failed to recognize the complex problems involved. Standard practice is to prescribe i.m. administration of a fixed dose of an opioid on a "PRN" (as required) basis. Thus a dose of analgesic is given, at the discretion of a nurse, on demand by a patient in whom the pain threshold has been exceeded. This type of regimen gives poor results for the following reasons:

(1) Responsibility for management of the patient is delegated from the anaesthetist to junior medical staff who, in turn, delegate responsibility to the nursing staff.

(2) Nursing staff vary widely in their degree of rapport with the patient and they may be too busy to deal immediately with a request for analgesia. Administration of opioids takes time because of the necessity for checking the drugs according to Controlled Drugs Act regulations. Nurses may withhold opioids because of fear of side effects, particularly respiratory depression, and the perceived potential for producing physical dependence. While there is little evidence to suggest that the treatment of acute pain with opioids for 2–3 days after operation is likely to cause addiction, respiratory depression remains a valid concern.

(3) In the absence of personal experience of the severity of postoperative pain, it is difficult for nursing staff to acknowledge the extent of a patient's suffering in the postoperative period.

Other major difficulties in the treatment of postoperative pain include:

(1) Difficulties in quantifying pain (see above).

(2) Difficulty in titrating doses of drug to a measured effect—there is no easily defined "endpoint".

(3) Analgesic requirements vary widely according to the type and severity of surgery.

(4) Analgesic requirements vary widely as a result of pharmacokinetic and pharmacodynamic variations between individuals.

(5) Administration of adequate doses of analgesics may be inhibited because of induction of side effects such as nausea and vomiting or respiratory depression.

Thus the list of disadvantages of the conventional method of administering i.m. opioids is daunting: the dose prescribed may be too small (inadequate analgesia) or too large (side effects); the technique results in widely fluctuating plasma concentrations of the drug; i.m. injections are painful; and the technique induces a feeling of dependency on the nursing staff. There are, however, some advantages of this conventional method. It represents familiar practice and thus may be inherently safe because of accumulated experience. It requires no special equipment and is therefore inexpensive, and the gradual onset of analgesia permits observation of the gradual onset of possible overdose.

Newer Approaches to Treatment

New drugs

As discussed above, it is unlikely that any of the current agonist/antagonist drugs represents a major advance on pure agonist drugs in most situations. Those with a low propensity for respiratory depression also have a low "ceiling" for analgesia.

New methods for old drugs

These techniques embody the philosophy that established agents are more effective if given in a manner which optimizes their action. To obtain effective analgesia, the aim is to maintain a steady-state plasma concentration of opioid in the region of the "minimum effective analgesic concentration" (MEAC (table IV)). As this varies widely between individuals, it is not possible to predict a dose regimen for a particular patient in advance of some assessment of that patient's susceptibility to opioids. With bolus i.v. and continuous i.v. techniques, the assessment of the patient's requirements is in the hands of the observer. With patient-controlled analgesia (PCA), a feedback loop is established whereby the patient controls his own plasma opioid concentration according to need.

Bolus i.v. administration. It is common practice to administer small i.v. boluses of opioid in the recovery room to produce analgesia in the period immediately after surgery. In the setting of the high-dependency area, this technique may be continued in the later postoperative period, and may be acceptable, providing there is a 1:1 nurse:patient ratio, to permit detection of respiratory depression. This technique produces wide fluctuations of plasma opioid concentration which may be lessened by continuous infusion or PCA methods.

If titrating an i.v. opioid against pain in the short term, it is inadvisable to use an agent with a slow onset, such as morphine or buprenorphine, unless the time to maximal effect of each increment (approximately 10 min) is observed before administering a further increment. In situations where rapid control of pain is desired, it is preferable to use an agent with a faster onset time such as fentanyl, diamorphine or pethidine.

TABLE IV. *Minimum effective analgesic concentration (MEAC) for some opioid drugs in plasma*

Agent	MEAC plasma concn (ng ml^{-1})
Morphine	16
Pethidine	455
Fentanyl	1
Alfentanil	10

Continuous i.v. infusions. Various authors have attempted to assess the patient's opioid requirements by means of small i.v. boluses until adequate analgesia is achieved. They then prescribed a fixed continuous i.v. infusion based on the initial quantity of opioid administered [10, 33, 34]. There are several problems associated with this technique, the most important being the potential for overdosage and respiratory depression, particularly if the initial assessment of opioid requirement did not take into account the slow onset of some drugs. More complex regimens have been developed which take into account the complex pharmacokinetics of opioids [3, 17, 40]. In the view of the authors, continuous infusion techniques based on observer control should be used only in high-dependency nursing areas where the inherent problems of respiratory depression can be rapidly diagnosed and treated. It is worth noting that hypovolaemia may cause a relative overdose of opioid if the initial assessment was made when the circulating volume was normal.

Patient-controlled analgesia (PCA)

The concept of PCA may be regarded as a simple closed-loop system. Unlike simple infusions, for which the observer determines the plasma concentration of drug, the patient determines the dose required to maintain adequate analgesia. The optimum plasma concentration, as determined by the patient, is that which satisfies his subjective requirement for analgesia while avoiding excessive dosage which would produce unacceptable side effects such as nausea and vomiting or such a degree of CNS depression which would by itself inhibit further activation of the apparatus.

The most basic form of PCA apparatus, such as the original Cardiff Palliator, administers a bolus dose of drug on receipt of a correctly delivered demand. The size of the bolus dose and the "lockout time" (the minimum time interval between doses) is set by the operator. The rate of infusion of each bolus can also be set. A problem with this form of apparatus is that, if the patient falls asleep and thus makes no demand for some time, the plasma concentration of analgesic decreases below the MEAC for that patient and the patient may waken in pain. It may then take several demands to restore adequate analgesia. Even so, it has been suggested that there is less disturbance of nocturnal sleep during PCA compared with conventional therapy [25].

To obviate this theoretical problem, other workers have developed machines which deliver a continuous low-dose background infusion on which the patient may superimpose additional demands for bolus doses. This philosophy was extended even further [17] by Hull in his development of the on-demand analgesia computer (ODAC) apparatus which will give 50% of the demand doses of the previous 1 h as a continuous infusion over the succeeding 1 h, thereby gradually decreasing the rate of continuous mandatory infusion as the patient's pain state gradually improves.

The problem with all continuous infusion strategies is the possibility of respiratory depression. In the original, experimental ODAC device, a pneumograph monitor was incorporated which inhibited the infusion if there was a 15-s period without respiratory movement. It has not been possible to incorporate this feature in the commercial version of the device. For safety, therefore, it may be best to accept a mandatory infusion rate which falls some way short of maintaining a steady-state plasma concentration close to the MEAC value, and allow supplementation by bolus demand.

The Cardiff Palliator is no longer available and has been replaced in the U.K. by the more sophisticated Graseby patient-controlled analgesia system which, like the on-demand analgesia computer, is a microprocessor-controlled pump which permits a background infusion in addition to patient-demanded boluses; however, the rate of the background infusion is operator-controlled. The philosophy of patient-controlled analgesia and development of apparatus has been reviewed [22, 25].

Efficacy of PCA. Although experience with PCA is expanding rapidly, especially in the U.S.A., its use has not become widespread in routine clinical practice in the U.K. Nevertheless, there are sufficient data to suggest that it represents a major advance in analgesic therapy in postoperative pain. Obviously, not all patients will be suitable for the technique: the very young and those who cannot comprehend what is required need an observer-based technique.

Most workers have reported consistent results with PCA: it has a high degree of patient acceptability and subjects tend to maintain a relatively constant plasma concentration of opioid (although there may be a 4–5 fold difference in concentrations between individuals). Dose requirements are generally smaller than the maximum which would be available if the same drug was given on a PRN basis. There is no suggestion that PCA leads to more side effects such as sedation, nausea or respiratory depression than conventional i.m. analgesia. However, cases of severe respiratory depression as a result of operator or machine error have been reported, and this emphasizes the need for full training in the technique for all staff concerned [35, 39, 41, 45]. Work from our department [43] suggests that the "low dose infusion + bolus" technique with morphine yields marginally better results than bolus alone.

Routes of administration. Most work with PCA has used the i.v. route. It is important that either a dedicated i.v. cannula or a one-way valve is used to ensure that each dose reaches the patient and does not accumulate by retrograde flow into an i.v. infusion. The i.m. and s.c. routes have also been used satisfactorily. Extradural administration of opioids has also been reported on a PCA basis, but this technique should be confined to high-dependency areas.

Other routes of administration of opioids

Oral. The use of sublingual buprenorphine has been considered above. The oral route of administration of drugs is the most widely used for all types of medication and is often the most acceptable to the patient. However, apart from minor ambulatory surgery and in the late postoperative period after more major surgery, the oral route of administration of opioid analgesics has several major disadvantages:

(1) Delay in gastric emptying is common after surgery. Because absorption of these drugs occurs from the small intestine, analgesia may fail because of lack of absorption. More seriously, the dumping of a large volume of drug into the small bowel when gastric motility resumes may result in overdose at a time when the patient may be under less close surveillance. Work with the slow-release tablet formulation of morphine (MST Continus, Napp Laboratories) after abdominal surgery confirms that absorption is delayed within the first 24 h of surgery [26]. Thus the use of this formulation is not recommended within 24 h of surgery.

(2) Nausea and vomiting in the postoperative period may preclude the use of oral medication.

(3) Because of considerable first-pass metabolism in the liver, the bioavailability of oral opioids is greatly reduced. Prediction of adequate dosage is

thus even more difficult than with parenteral administration.

Although some reports have stated that adequate analgesia may be achieved using this route, the oral route is generally regarded as unsuitable for the administration of strong opioids in the early postoperative period.

Rectal. The use of rectal diclofenac and meptazinol has been noted above. Rectal administration of drugs is relatively unpopular in the U.K., but this route does possess some advantages:

(1) Absorption of drugs from the lower part of the rectum bypasses the portal venous system. Drugs absorbed in the upper rectum pass into the superior rectal vein and are, therefore, subject to first-pass metabolism. The overall bioavailability may thus depend on the siting of the preparation in the rectum.

(2) Absorption of drugs is unaffected by delay in gastric emptying, or by nausea and vomiting.

(3) Administration of the drug may be discontinued simply by removal of the suppository.

The rectal route has been used with sustained-release preparations of morphine (the morphine hydrogel suppository) and this technique may be useful in producing a low sustained plasma concentration of the drug which can be augmented by further systemic doses [14].

Transdermal. Transdermal administration of drugs is now well established in therapeutics, and suitable delivery systems for glyceryl trinitrate have been available for several years. Recently, a transdermal delivery has been developed for fentanyl, and encouraging results have been obtained in the treatment of postoperative pain [32]. Holley and Van Steennis [16] and Duthie and colleagues [11] reported that the TTS-fentanyl patch (TTS = transdermal therapeutic system) was capable of providing an analgesic plasma concentration of fentanyl. The product is designed to provide a sustained release of 100 μg h^{-1}. However, it should be applied 2 h before the expected painful stimulus and a bolus of i.v. fentanyl is necessary as a loading dose.

SAFETY CONSIDERATIONS

Although traditional PRN methods of administering postoperative analgesia may be inadequate, they do have the merit of simplicity and familiarity in use which provide a degree of inherent safety. New techniques and drugs must be shown not to entail any unjustifiable hazard to the patient. When dealing with opioid drugs, the overriding concern of the prescriber is the avoidance of dangerous respiratory depression.

Monitoring of respiration

The maintenance of adequate pulmonary gas exchanges is obviously essential to life. Unfortunately, it is difficult to make a simple bedside judgement of the adequacy of ventilation, especially in the sleeping subject.

The work of Holley and Van Steennis [16] confirmed previous observations that random counting of ventilatory rate does not correlate with the presence of hypercapnia. In a study with i.v. and transcutaneous fentanyl, subjects with $Pa_{CO_2} > 6.7$ kPa had ventilatory rates varying from 7 to 22 b.p.m.; conversely, in subjects with ventilatory rates of 10 b.p.m. or less, Pa_{CO_2} values ranged from 3.3 to 7.1 kPa. Catling and colleagues [10] observed a high incidence of episodes of arterial oxygen desaturation during continuous opioid infusions in postoperative patients and emphasized the need for continuous oxygen administration in these patients: this was found largely to obviate decreases in saturation.

If simple observations do not suffice, what may be utilized? Pulse oximetry detects arterial oxygen desaturation but, in the presence of supplementary oxygen, may not detect mild respiratory depression. Electromechanical strain-gauge devices may be used for continuous monitoring of chest-wall movement, but may not detect the presence of an obstructed upper airway. In practice, however, continuous monitoring with the pulse oximeter is probably the safest method of assessment.

It should be noted that there is some debate on the incidence of significant sleep apnoea in the normal population [6], although there is general agreement that the condition is commoner in males, in heavier subjects and with increasing age.

THE ACUTE PAIN SERVICE

The deployment of more sophisticated forms of acute pain relief (local anaesthetic techniques, extradural opioids, PCA) has been constrained by the facts that these techniques may be time-consuming and that correct application requires specialist skills and knowledge. Ready and colleagues [29] have described their experience with an Acute Pain Team to supervise patient-controlled analgesia and extradural opioid analgesia. It may be difficult to provide a similar service elsewhere because of manpower constraints, but many of the advantages of this type of service could be obtained by greater stratification of patient care in hospital. The provision of high-dependency units, which would concentrate on the provision of care for patients in the immediate postoperative period, would greatly facilitate the use of effective analgesic techniques and may allow the more efficient deployment of nursing and medical staff.

In conclusion, we have attempted to examine some of the recent advances in postoperative analgesia using systemic drugs. Perhaps the most important task we have is to heighten awareness of the size of this problem and to ensure that all staff are aware of the variables involved. Most patients in hospital will continue to receive i.m. opioids because of the simplicity of, and familiarity with, this technique. However, the introduction of simple methods of pain scoring and a greater degree of flexibility in the administration of opioids would lead to considerable improvement in acute pain therapy.

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Br. J. Anaesth. (1989), **63**, 159–164

DEVELOPMENTS IN LOCAL ANAESTHETIC DRUGS AND TECHNIQUES FOR PAIN RELIEF

J. A. W. WILDSMITH

Role of local anaesthesia in pain relief

Many anaesthetists working in chronic pain clinics become involved in that field because of an interest in nerve blockade. While the techniques may have diagnostic, prognostic and therapeutic roles, especially in pain associated with organic disease, a number of other skills are needed. Many patients have behavioural or psychological factors contributing to, or even the main cause of, their pain and nerve blocks have a decreasing role in its management [39]. Psychological factors have a relevance even when the pain is acute, but the single most important factor is tissue damage, particularly if this is the result of surgery or some other factor that has a limited duration because of the effects of healing.

Because the majority of nociceptive stimuli arise peripherally, nerve blocking techniques can be very effective in the management of acute pain and could be used much more widely than they are at present. Regional anaesthesia has many features that can, if properly used [6], be to the patient's advantage. None of these features is more impressive than the profound analgesia that is produced in the early postoperative period. Many dismiss the use of single injection techniques because their duration of action is limited, but this ignores the failure of systemic drug therapy to relieve early postoperative pain in particular [17].

The solution to this problem is to encourage the *sequential* use of analgesic methods. The block provides profound analgesia, not only during, but also for a period of time after the operation. Subsequently, systemic drugs (with their administration timed so that they become effective *before* complete regression of the block) may produce acceptable relief of the pain because its intensity gradually lessens. The aim should be to match the method to the amount of pain the patient is likely to experience. Such an approach has been shown to produce improved pain relief and fewer respiratory complications after cholecystectomy in two separate investigations. One study used continuous extradural block for 12 h after surgery [12], and the other a single injection intercostal block technique [13]. Both studies showed the regional technique to be superior to conventional "on demand" i.m. opioid analgesia and the extradural study also found it better than the continuous i.v. infusion of morphine.

A major fear of the prolonged use of extradural techniques is hypotension resulting from sympathetic block. Clear strategies for preventing and treating hypotension must be available to the staff caring for the patient, but it is important to consider also the benefits of sympathetic block. Thrombo-embolic disease is still a major cause of surgical morbidity and mortality, with venous stasis in the lower limbs being a major predisposing factor. A comparative study of extradural block and i.v. diamorphine, both given to produce total relief of pain after gynaecological surgery, examined their effects on calf blood flow [5]. Extradural bupivacaine produced a major increase in calf blood flow, but i.v. diamorphine did not affect it (table I). Interestingly, the decreases in arterial pressure produced by the two analgesic regimens were very similar and of little clinical significance.

In addition to the effect of sympathetic nerve block on blood flow, local anaesthetic drugs may also decrease the risk of thrombosis by modifying the changes in coagulation induced by surgery. For many years, i.v. lignocaine has been known to have a primary antithrombotic action [9]. More recently a comparison of extradural bupivacaine

TABLE I. *Mean changes in calf blood flow and mean arterial pressure in two groups of patients with analgesia provided by extradural bupivacaine or i.v. diamorphine. (Data from Bowler, Lamont and Scott* [5])

Analgesic method	Flow	MAP (mmHg)
Extradural bupivacaine	+64%	95 (81)
I.v. diamorphine	No change	94 (85)

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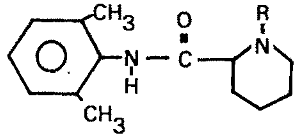
and i.m. opioid for postoperative analgesia after hip surgery showed that the extradural technique produced enhanced fibrinolysis and an antithrombotic effect [25].

PHARMACOLOGICAL DEVELOPMENTS

To provide the maximum benefit, agents with a long duration of action are obviously required for single injection techniques, bupivacaine being the current agent of choice. Its long duration also means that the risk of cumulative toxicity is low during continuous techniques. It is also recognized as having a more immediate effect on pain transmission than other local anaesthetic drugs, and is non-irritant—a feature that is not shared by all potentially long acting local anaesthetic agents [21]. However, the safety of bupivacaine has been in some dispute since Albright raised the issue of primary cardiotoxicity with the longer acting local anaesthetics [3].

Initially there was some scepticism that a drug from a group known to have anti-arrhythmic actions could actually produce arrhythmias in the absence of hypoxia. Hypoxia could certainly have played a part in many of the cases reported, but evidence gradually emerged [10] that the therapeutic ratio of bupivacaine is narrower than for the other drugs. Under certain circumstances (rapid i.v. injection of a large dose, especially in the obstetric patient) bupivacaine can produce primary ventricular fibrillation which is difficult to treat. The likely mechanism was thought to be a direct effect on the myocardium, but central stimulation of the autonomic nervous system was also considered to be a possibility. Subsequent investigation has confirmed and quantitated these features [36]. On an equipotent basis, bupivacaine has the same effect on myocardial contractility as lignocaine, but it has four times the ability to produce ventricular arrhythmias. The possibility that this effect is mediated centrally, and as a result of massive sympathetic discharge, has yet to be ruled out.

The risk of this complication occurring clinically exists only if a large dose is injected rapidly into the circulation, so prevention should be easy. Aspiration tests are essential and many would consider that a test dose is essential, although bitter experience has shown that neither will guarantee that the catheter is properly placed. At the start of the block the first dose should be given slowly in increments, with careful questioning of the patient for the early features of systemic effect [42]. For many procedures a catheter, so often the factor responsible for an i.v. injection, may be superfluous [47], but if one is needed it may be wiser to institute the block with a "safer" drug such as lignocaine (especially in the obstetric patient). Thereafter the block may be continued with small increments or an infusion of bupivacaine.



	R	p*K*a	C'LogP
Mepivacaine	$-CH_3$	7.7	2.6
Ropivacaine	$-C_3H_7$	8.1	3.7
Bupivacaine	$-C_4H_9$	8.1	4.2

FIG. 1. General structural formula for the amino-acyl-amide group of local anaesthetics and details of three members of the series. C'LogP = a theoretical index of lipid solubility which is related to potency.

There is the possibility of less toxic, long acting drugs becoming available. Ropivacaine is a member of the same chemical series as bupivacaine, but has a propyl radical attached to the amine group (fig. 1). It has the same pK_a as bupivacaine, but a slightly lower lipid solubility. It would thus be expected to be slightly less potent and shorter in duration of action than bupivacaine, but animal work suggests that it has a vasoconstrictor effect that compensates for this [2]. Comparative studies in volunteers [Scott and colleagues, in preparation] have shown that ropivacaine has favourable pharmacokinetic properties and, perhaps more importantly, a less marked electrophysiological effect on the heart (table II). Early clinical results are promising.

TABLE II. *Mean changes in stroke volume (SV) (measured by echocardiography) and Q–T interval in a group of six volunteers given i.v. infusions of bupivacaine or ropivacaine on two separate occasions. The infusions were discontinued when early subjective features of systemic toxicity became apparent. (Data from Scott and colleagues, in preparation)*

Drug	Dose (mg)	SV	Q–T
Bupivacaine	99	−16%	+7%
Ropivacaine	124	−16%	+1%

It remains to be demonstrated if ropivacaine has a differential blocking effect on pain impulses similar to that of bupivacaine. This property seems to relate to the ability of bupivacaine to block C fibres more rapidly than A fibres when the drug is applied to an isolated nerve preparation. It also produces very marked frequency-dependent block of C fibres when the preparation is stimulated at frequencies close to those seen *in vivo* [48]. A drug such as etidocaine, which is known to produce very profound motor block in clinical practice, blocks A fibres faster than C in such experiments and its action is not influenced to quite the same degree by rapid stimulation of the preparation. Given the similarity in structure, it is not surprising that the laboratory evidence concerning ropivacaine suggests that it is much closer to bupivacaine than etidocaine.

Whatever the final position of ropivacaine, bupivacaine will remain the only readily available, long acting agent for some time. It is to be hoped that its careful use will avoid major toxic reactions, but users of bupivacaine must be ready to treat them. The initial priority is effective ventilation of the lungs and oxygen. Often, any convulsions stop before an anticonvulsant can be given, but if one is needed, it is important to limit its dosage to minimize further cardiorespiratory depression. If cardiac arrest does occur, cardiac massage may need to be continued for a very long time and repeated attempts made at defibrillation. The essential electrophysiological problem is a prolonged refractory period, which adrenaline will shorten. To the same end, metabolic acidosis must be corrected. Because the prolonged refractory period allows "re-entry" type arrhythmias known as "Torsades de Pointes", the treatment of choice if the other measures fail is bretylium in large doses (5–10 mg kg^{-1}) [18].

DEVELOPMENTS IN TECHNIQUES

The pain pathway may be interrupted by injection of local anaesthetic drugs at a number of different levels—infiltration, peripheral, plexus, extradural and subarachnoid blocks could all be used. Choice between these methods will depend on a number of factors. The site and type of operation are obvious ones, and choice may be further limited by some feature of the patient. A common argument against major blocks for postoperative analgesia is that nursing workload is increased so that the available facilities will be overstretched. It is the author's view and experience (both are shared by his nursing colleagues) that the patient who has a continuous extradural block after major surgery is in fact easier to look after. Such arguments are too often put forward to cover a deficiency in technical expertise (an obvious major factor affecting the choice of method) or in commitment to better pain management.

Central block

Currently, the subarachnoid route is not used for the continuous administration of local anaesthetic drugs to produce postoperative analgesia; the potential of the method is considered later. For abdominal and thoracic surgery, the present "gold standard" is of course extradural block by continuous infusion. Massey Dawkins was the pioneer of this method of postoperative pain control and, more than 20 years ago, he recognized that it was essential to place the catheter at a dermatomal level appropriate to the incision [15]. Many do not appreciate this now. For example, the catheter should be inserted at about the 6th thoracic space if the incision is to be in the upper abdomen. With a controlled infusion (0.125% bupivacaine 10–15 ml h^{-1}) producing a constant level of block, the arterial pressure is usually very stable. This is because the circulation can usually adapt very well to a constant degree of sympathetic block, *as long as the patient does not become hypovolaemic*. The care of such patients is not more difficult than that of a patient receiving conventional analgesia, but the emphasis of that care is different [4].

Thoracic nerve block

For unilateral procedures to the chest or abdomen, block of the thoracic nerves at some part of their course is a very attractive alternative to central block [23]. In recent years there has been some controversy, based on a number of anatomical, radiological and clinical studies, regarding the possibility of blocking several nerves with a single injection [7, 11, 26–32]. The consensus view from these studies seems to be that this is possible, but that the main route of spread is along the paravertebral space (fig. 2). Even so, this will occur reliably only if the injection is made at or medial to the angle of the rib. As with the continuous extradural technique, it is important to make the injection (or insert the catheter [27]) at a space appropriate to the level of the wound. Impressive results have been de-

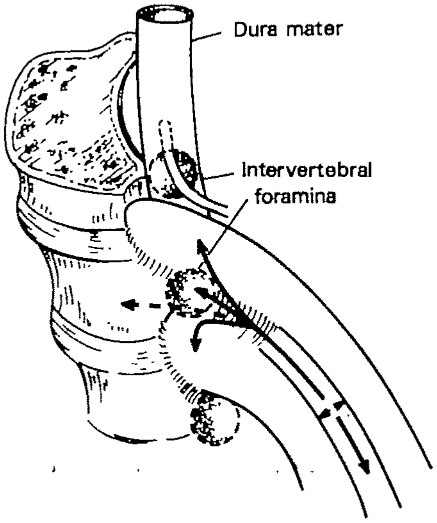


FIG. 2. Potential routes of spread of local anaesthetic solution after injection in the intercostal space. Mowbray, Wong and Murray [28] found spread to 1–2 intercostal spaces and 2–5 paravertebral spaces after injecting 20 ml at the rib angle. They did not observe spread into the intervertebral foramina, but occasionally there was spread across the anterior surface of the vertebra (the dotted line) to the opposite paravertebral space.

scribed after single, more lateral injections, but these have usually been in patients who have suffered trauma, and who have disruption of the normal anatomical barriers to spread of solution.

The other possibility is that such single injections have been made into the pleural cavity without it being appreciated that this has happened. A group in Norway have been claiming remarkably good results for a technique in which they deliberately insert an extradural type catheter into the pleural space and make repeated injections [35]. It is assumed that the local anaesthetic diffuses through the somatic pleura and into the intercostal nerves. Certainly, studies of the disposition of fluid injected into the pleural cavity have shown that it tends to accumulate in the paravertebral area [24] where the nerves are covered only by the somatic pleura [20], so this mechanism is a very likely one. The technique has also been used successfully in the management of patients with chest trauma [37], but has been found to be less useful after thoracotomy [38]. However, it may be that the local anaesthetic solution escaped through the chest drain before it could have any significant effect in the thoracotomy study. With this exception, most of the published reports have considered the method to be very effective.

It is usual to insert the catheter through an extradural needle at the 7th thoracic space—the pleural cavity being identified by the loss of resistance technique. The potential for causing a pneumothorax is obvious and, although this complication seems surprisingly uncommon, it has been described [37]. If the technique were to be used more widely by less skilled personnel, the incidence of pneumothorax might increase considerably. It would certainly seem more sensible to use a lower space than the 7th, so that the needle is inserted below the edge of the lung, but above the pleural reflection [45].

The other potential complication is systemic toxicity caused by the local anaesthetic. The recommended bolus dose is 20 ml of 0.5% bupivacaine with adrenaline 1:200000. This is said to have a mean duration of approximately 11 h, but the effect may be much shorter and systemic toxicity has been reported [41]. This risk may be lessened by the use of continuous infusions, which have been used with good effect in adults [37] and children [22]. This is a technique that needs much more evaluation to establish its effectiveness and safety.

Peripheral nerve block

Catheter techniques may also be adapted for use with the major upper [16] and lower [44] limb blocks to provide "continuous" analgesia. As with the central blocks, these techniques require a certain amount of expertise and commitment, but it is possible to improve considerably the comfort of many of our patients with much simpler blocks. Infiltration of a pseudarthrosis has been shown to be very effective after orthopaedic procedures [33], and the topical application of local anaesthetic gel may well be the optimum method of providing analgesia after circumcision [44]—simple, effective, repeatable and affecting no neuronal function other than the source of the pain. Spraying bupivacaine onto the donor site of a split skin graft before application of the dressing is also very effective. All that is needed is the commitment to incorporate the method into the theatre routine. Such relatively simple techniques may even be useful after laparotomy [19], and require further evaluation.

These blocks would be insufficient for the actual surgery, but as a supplement to general anaesthesia have a great deal to offer. This is not to condone what has been described as "bupivacaine squirting" [8]. This involves the rather vague, general infiltration of the wound area, with little attention being paid to the source of the pain, the innervation of the wound or the proper performance of aspiration tests.

FUTURE DEVELOPMENTS

Since the discovery of opioid and other receptors in the spinal cord, a wide range of drugs has been injected into the spinal canal. Potentially, these are very exciting developments, but relatively little attention has been given to the local effects, whether pharmacological or toxicological, of these agents. For instance, the commercial preparation of fentanyl will, when applied to a peripheral nerve preparation, produce complete block of impulse transmission in a few minutes [34]. Recovery is only partial when the solution is washed from the nerve because it is very hypotonic and thus neurotoxoic. Any solution injected near a nerve must be both isotonic and non-irritant.

In fact fentanyl (even in isotonic solution) blocks nerve conduction [34], as do other opioids, so it must be recognized that their effect in central nerve block may be the result of modulation of nerve, as well as synaptic, function. The fact that one drug can possess these two actions opens up an interesting possibility. One agent could produce both local anaesthesia for surgery and prolonged spinally mediated analgesia thereafter. Pethidine actually has the appropriate balance of activity, and there have been several reports of its intrathecal administration [1, 14, 40, 46]. It produces an "anaesthetic" block described as comparable to that achieved with hyperbaric lignocaine and excellent subsequent analgesia, with evidence of respiratory depression only when a large dose is used. The complicating factor is that pethidine has always been considered a tissue irritant [46] and it would be unwise to use it intrathecally until this has been fully re-evaluated.

When drugs are administered intrathecally, considerable effect is produced by very small doses. The development of the use of the opioids by this route is a pointer to how current work on the pharmacology of the spinal cord may produce entirely new strategies for the management of acute pain.

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Br. J. Anaesth. (1989), **63**, 165–188

THE RATIONAL USE OF INTRATHECAL AND EXTRADURAL OPIOIDS

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The prime function of anaesthetists is to relieve pain. The technical skills and pharmacological knowledge required to do this during surgery place them in an ideal position to treat pain in other situations. Thus anaesthetists have been at the forefront of developments in the relief of pain during labour and devote much attention to the relief of chronic pain of whatever aetiology. Indeed, active societies exist in both these disciplines and have been vigorous in the promotion of research and teaching, even though such activities are expensive in terms of time and manpower.

Postoperative pain relief, however, has been sadly ignored [189] and members of the public [114], and even eminent members of the profession [67, 162], have been moved to comment on the severity of pain after surgery and the lack of efforts to relieve it. The standard method of prescribing a fixed dose of opioid to be given at limited time intervals, and with administration being delegated to a nurse, is manifestly a totally inadequate method of producing postoperative analgesia. Extradural block with local anaesthetic agents will abolish postoperative pain, but its use has been limited by anxiety about hypotension, tachyphylaxis, systemic toxicity, the technical difficulty of insertion of a catheter into the thoracic extradural space and the problems of postoperative surveillance. Other nerve blocks, particularly intercostal [125], can also be very successful, but their use is restricted by the feasibility of repeating them in the postoperative period.

Patient controlled analgesia was introduced in an attempt to overcome many of these problems and has proved to be a successful method after surgery [39, 182]. It can also be used as a method by which the efficacy of other analgesic techniques may be assessed by registering the number of demands for additional analgesia [115]. However, it does require the use of sophisticated and relatively expensive apparatus and the maximum dose of drug and minimum time interval between doses are set by the doctor, who must err on the side of safety in these choices. Experience of such apparatus has indicated that the patients chose a balance between analgesia and the incidence and severity of side effects.

The discovery of opioid receptors in the central nervous system, in particular their existence in the spinal cord, came at an opportune time and raised exciting new possibilities in the management of severe pain.

HISTORICAL BACKGROUND

The steps leading to the eventual use of spinal opioids in man are shown in table I. In 1976, Yaksh and Rudy [206] showed, in rats, that opioids applied directly to the spinal cord and remaining localized, produced intense analgesia. It was suggested [204] that the receptors through which the drugs were acting were situated presynaptically on afferent terminals in the substantia gelatinosa and that the effect was to block the release of the neurotransmitter associated with nociceptive transmission [96]. In this region,

TABLE I. *Historical background to use of spinal opioids in man*

1971	Demonstration of existence of opioid receptors [82]
1973	Demonstration of opioid receptors in the brain [148]
1976	Demonstration of opioid receptors in the spinal cord [105]
	Demonstration in animals of analgesia produced by spinally applied opioids [206]
1979	Intrathecal opioids first used in man [193]
	Extradural opioids first used in man [18]

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TABLE II. *Predicted advantages of spinally applied opioids*

Segmental analgesia with no sensory or motor loss.
No autonomic block with consequent absence of hypotension.
No central or respiratory depression.
Availability of a large number of drugs.
Existence of a specific antagonist.

opioids have been shown *in vivo* to antagonize the release of one putative transmitter, substance P [205]. In 1979, morphine was used intrathecally [193] and extradurally [18] in man, and in small doses produced prolonged analgesia in patients with chronic pain.

A number of advantages were predicted for this new method of analgesia (table II). It was hoped that segmental analgesia would be produced by only small doses of drug, without loss of any other sensory modality or interference with motor function. There should be no autonomic block and hence no hypotension, which is the main factor limiting the use of extradural local anaesthetics; there should also be no interference with bladder function. Inadvertent intravascular injection would be unlikely to have the serious consequences associated with i.v. local anaesthetics. Above all, was the possibility of divorcing respiratory depression from analgesia with opioid drugs. A range of opioids was available, the different durations of action of which would match different clinical situations. Finally, a specific antagonist was already available in the form of naloxone, thus guaranteeing prompt antagonism of any unwanted sequelae.

After the first reports, there was a surge of publications attesting to the efficacy of this new technique. Winnie [200] commented that never before had sophisticated laboratory research moved so rapidly into the clinical field. Unfortunately, many of these initial reports ignored the fundamental principles of properly conducted clinical trials, and claimed complete analgesia of very prolonged duration with no complications. One of the main reasons for this was the lack of any "central" control for the studies that were being performed, because there was no requirement for such control: neither the drugs nor the techniques were new; it was the application that was new [200].

The purpose of this review is to produce some logical conclusions on the use of spinal opioids and consideration will be confined to their use in acute pain. In order to do this it is necessary to:

(1) verify the points documented in table II
(2) make some comparison of the available drugs
(3) assess the merits of the extradural compared with the intrathecal route of administration
(4) compare extradural and intrathecal opioids with other methods of analgesia
(5) assess the nature, incidence and severity of complications.

ANALGESIC EFFECTS

Extradural Opioids

There is no doubt that opioids injected into the extradural space produce effective and often prolonged analgesia. Pethidine 100 mg in normal saline 10 ml was first used for postoperative pain in seven patients [55]. Onset of analgesia was rapid and complete between 12 and 20 min after injection. At this time, blood concentrations of pethidine were less than those necessary to produce analgesia, and concentrations in cerebrospinal fluid (CSF) were high. Pain relief lasted an average of 6 h and there was no evidence of sensory, motor or autonomic block.

Morphine, in doses varying from 2 mg [161] to 0.1 mg kg^{-1} [195], has been the most widely used drug. Analgesia tends to be slow in onset, taking up to 60 min [59, 121, 195] to develop, but can last for more than 24 h, with many reports mentioning that only one injection was required after operation. No evidence of block of any other sensation or of motor power has been revealed by these studies and hypotension has not been a problem.

Available evidence confirms that analgesia results from a regional rather than a systemic effect, although there may be some initial contribution from the latter. Pharmacokinetic studies have found no relationship between quality of analgesia and plasma concentrations of the drug, which have been well below reported "analgesic" concentrations [134, 178, 195, 208]. Indeed, excellent analgesia may be present with no morphine detectable in the plasma. Experimental work in volunteers also confirms the segmental effect of extradural morphine. Torda and colleagues [188] found that morphine 3 or 4 mg injected into the lumbar extradural space resulted in an increase in pain threshold in the legs, but not on the forehead, while i.m. morphine raised the threshold in both areas. Similarly, extradural morphine 3.5 or 7.5 mg markedly delayed the onset of experimentally induced ischaemic pain in the lower limbs, but not in the arms. This effect was still present 6 h after injection [185]. Subcutaneous morphine had no significant effect on the times to pain perception in either limb and the authors concluded that the extradural morphine produced analgesia by a regional effect rather than by systemic absorption.

A greater improvement in postoperative pulmonary function has been found by workers who compared extradural opioids with other analgesic techniques. Bromage, Camporesi and Chestnut [27] found that extradural opioids were more effective than i.v. morphine in restoring FEV_1 towards preoperative values. Rybro and colleagues [168] found that 67% of patients who received i.m. morphine after upper abdominal surgery had radiological changes on chest x-ray on the 2nd day after operation, compared with 21% who had received 4-mg doses of morphine extradurally. After cholecystectomy, analgesia with extradural morphine resulted in a smaller decrease in peak expiratory flow than was associated with either i.m. opioids or intercostal block with bupivacaine [157]. Bonnet and colleagues [24] found lower pain scores with extradural morphine than with i.m. injections of the analgesic baralgine, but no difference in VC, FEV_1 or FRC. A decrease in postoperative morbidity [177] and possibly mortality [207] has also been reported. However, Hjortsø and colleagues [89], using a mixture of extradural morphine and bupivacaine, found that although pain scores were lower than with i.m. morphine after abdominal surgery, there was no difference between the groups in terms of postoperative mortality, pneumonia, arrhythmias, wound complications, deep vein thrombosis or convalescence.

Dose of morphine

Despite the widespread use of extradural morphine there have been few dose finding studies. Morphine 2 mg is effective in relieving pain after lower limb orthopaedic surgery [121, 161], but ineffective after upper and lower abdominal surgery [57, 167]. However, 5 mg and 10 mg produced prolonged analgesia after lower abdominal operations, although no additional benefit resulted from the larger dose [57]. In particular, very prolonged analgesia has been noted to follow morphine 5 mg after Caesarean section [202]. Martin and colleagues [121] compared five doses of morphine (0.5–8.0 mg) after orthopaedic surgery and found that doses of 2.0 mg and greater were equally effective. Similar results were found by Lanz, Kehrberger and Theiss [106], who found that patients who received 2.0 mg or more were less likely to require additional analgesia. However, they also found that the incidence of urinary retention and pruritis increased dose dependently, and recommended 3.0 mg as being the best compromise between analgesia and an acceptable incidence of side effects. A dose of 4 mg produced excellent analgesia following hip arthroplasty and major lower limb surgery, but 6 mg was required in the thoracic extradural space after laparotomy or thoracotomy [181].

The majority of workers have used a fixed dose of morphine to produce analgesia after operation. In view of the known very wide variation in the individual response to opioids, it would seem much more rational to titrate the dose until the desired effect is reached. This approach was used by Bromage, Camporesi and Chestnut [27] when comparing three opioids (morphine, hydromorphone and methadone), extradural local anaesthetics and i.v. morphine for pain relief after upper abdominal surgery. They found that the dose of extradural morphine required to produce effective analgesia was very similar to that used i.v., but that the former route produced much more prolonged analgesia with significantly less central depression. Recently, patient controlled analgesia has been used by the extradural route [178]. Morphine in increments of 1 mg, with a minimum interval of 30 min between doses, or pethidine 20 mg, both produced satisfactory analgesia, there being no difference between the drugs. The authors did comment that large interindividual variations made it impossible to recommend a standard dose of either drug for analgesia of predictable duration and with a minimum of adverse effects.

Other drugs

Most narcotic analgesics have been used extradurally in the management of postoperative pain, by either bolus injection or continuous infusion (table III) and effective analgesia has been reported after the use of them all. Fentanyl has been given using a patient controlled system, when no difference was found in fentanyl usage between the extradural and i.v. routes [74]. Meptazinol 90 mg was found by Verborgh, Van Der Awera and Camu [191] to produce effective analgesia, but others found smaller doses to be ineffective and did not recommend its use [22,

TABLE III. *Opioids used extradurally*

Drug	Dose range	Reference
Pethidine	25–100 mg	[31, 55, 70, 81, 167]
	0.75 mg kg^{-1}	[145]
	1.0 mg kg^{-1}	[164]
Diamorphine	0.5–10.0 mg	[14, 16, 116, 120, 137]
	0.1 mg kg^{-1}	[94]
Fentanyl	100 μg	[167]
	200 μg	[112]
	20–80 μg h^{-1}	[19, 47, 198]
Alfentanil	200 μg h^{-1}	[47, 48]
	15–30 μg	[42]
Sufentanil	15–75 μg	[51, 65, 66, 117]
	3 μg kg^{-1} h^{-1}	[43]
Lofentanil	5 μg	[21]
Methadone	4–6 mg	[17, 197]
Buprenorphine	60–300 μg	[21, 107, 128, 129, 201]
Hydromorphone	1 mg	[45]
Meptazinol	30–90 mg	[22, 76, 191]
Butorphanol	1–4 mg	[2, 101, 183]
Phenoperidine	2 mg	[116]

76]. Lofentanil produces very prolonged analgesia, but because of its extreme potency and very strong receptor binding characteristics, concern has been expressed that antagonism might be difficult [21].

It would seem more sensible to use the shorter acting drugs like fentanyl by continuous infusion, particularly after upper abdominal surgery, where it produces effective, but short lasting analgesia when given by bolus injection [167]. Welchew and Thornton [198] found that an extradural infusion of fentanyl at a rate of 60 μg h^{-1} provided pain relief superior to that obtained with i.m. papaveretum. An infusion rate between 80 and 130 μg h^{-1} was necessary to maintain adequate analgesia after abdominal aortic aneurysm surgery [19]. These authors commented that the short duration of action of fentanyl actually aided bed management in the intensive care unit, since it was not necessary to keep patients in the unit for so long after the last injection. Alfentanil would probably be an even better choice, and has been shown to produce excellent analgesia after major abdominal surgery, although experience with its use is limited [47, 48]. Despite its long duration of action, continuous infusions of morphine have been used to manage postoperative pain in doses varying from 100 to 400 μg h^{-1} [58, 72, 73, 111].

Comparisons between the different opioids have been few, but it is unlikely that there will be any differences in analgesic efficacy between the drugs, but only in rate of onset, duration of action and incidence and severity of side effects. A major problem in comparing agents will be in choosing equipotent doses, because equivalent doses for systemic administration may well not apply to the extradural route. This has been shown to be the case for morphine and pethidine [178]. Thus Torda and Pybus [187] compared extradurally administered morphine 6 mg, methadone 6 mg, pethidine 60 mg and fentanyl 60 μg—doses which are regarded as being equipotent when given parenterally. There was no difference in the quality of analgesia, but the respective durations were 12.3 (SD 7.69) h, 8.7 (SD 5.89) h, 6.6 (SD 3.32) h and 5.7 (SD 3.72) h. No difference in the quality of analgesia was found between morphine and diamorphine [194].

Timing of injection

The efficacy of extradural morphine might be increased if it is given before the onset of pain [106]. The time to the first administration of an analgesic after surgery was almost twice as long in patients who had received extradural bupivacaine containing morphine 10 mg for the operative procedure than when bupivacaine was used alone [41]. In contrast, extradural morphine given for the first time on the day after surgery failed to produce useful analgesia. It has also been noted that morphine 5 mg given after chloroprocaine with adrenaline had been used for Caesarean section had a slower onset and provided poorer analgesia than when plain chloroprocaine was used [150]. This resulted from the greater acidity of the local anaesthetic combined with adrenaline, resulting in a greater degree of ionization of the morphine. Others have found that morphine [86, 166] and diamorphine [137] given extradurally before surgery reduced opioid requirement in the immediate postoperative period.

Effect on the stress response

Neither morphine [166] nor diamorphine [137] administered extradurally influences the metabolic and hormonal responses to surgery, although cortisol concentrations were lower than controls in the postoperative period, probably reflecting the better pain relief. Extradural local anaesthetics suppress the increase in catecholamine concentrations noted in the immediate postoperative period, whereas extradural morphine can only suppress this response later on, indicating that pain might be a factor in the production of the stress response [166].

Site of extradural injection

It was originally stressed that the segmental nature of the analgesia produced by extradural opioids demanded the use of thoracic injection after thoracic and upper abdominal surgery. The thoracic approach is more difficult anatomically than the lumbar and potentially more dangerous [135], but there are numerous reports of the lumbar route providing satisfactory analgesia after upper abdominal and thoracic surgery [84, 134, 136, 197]. However, Sandler, Chovaz and Whiting [171] commented on the long latency between the injection of lumbar morphine and pain relief in the thoracic dermatomes. This may lead to additional doses of drug being given before they are necessary, so that complications are more likely to occur. Caudally administered morphine has provided satisfactory analgesia after perineal [25, 151] and even cardiac surgery [165].

The explanation may lie in the properties of morphine. It enters the CSF but, being of low lipid solubility, does not rapidly enter the spinal cord; it may thus spread widely and produce diffuse analgesia. After thoracic extradural morphine, the drug quickly appears in the CSF at lumbar level [132]. In contrast, a lipid soluble drug would rapidly enter the CSF and be more rapidly absorbed into the spinal cord and would be expected to produce a more sharply segmental analgesia. Controlled studies have not been performed to verify this hypothesis, and few have compared the effects of thoracic *v.* lumbar extradural morphine for upper abdominal surgery. Asari and colleagues [10] found that the analgesia produced by thoracic morphine was significantly superior to that given in the lumbar region. In contrast, a retrospective study [78] found no difference between the two routes in the number of patients requesting additional analgesia, but there was a considerable discrepancy in the numbers (92 thoracic *v.* 30 lumbar) and such studies cannot give any indication of the quality of analgesia. Similarly, Larsen and colleagues [109] reported no difference between thoracic and lumbar morphine 5 mg after upper abdominal surgery, but the first assessments were not made until 6 h after injection.

Intrathecal Opioids

Intrathecal opioids also produce satisfactory and prolonged relief of postoperative pain [131]. Originally, doses of morphine as large as 15–20 mg were used [170], but although analgesia is significantly longer with these large doses, the incidence of side effects is also significantly higher [169].

Most workers inject morphine intrathecally before the surgical procedure and have found similar results. When 0.8 mg was given intrathecally before cholecystectomy, less papaveretum was required in the first 24 h after operation than in a control group [69]. O'Neill and colleagues [139] found that intrathecal morphine 1 mg resulted in a significant decrease in the need for postoperative analgesia after spinal surgery. Intrathecal morphine 0.8 mg provided analgesia during aortic aneurysm surgery that was indistinguishable from moderate doses of parenteral opioids and was no more effective in attenuating the autonomic responses during the procedure [61]. The principal advantage was the avoidance of irregular and inadequate analgesia in the early and the most painful part of the postoperative period. Isaacson and colleagues [92] found that patients given morphine 0.5–1.0 mg intrathecally before abdominal aortic surgery could be extubated earlier in the postoperative period and had significantly shorter stays in the intensive care unit and in hospital. Others have confirmed that earlier extubation is possible after major abdominal surgery when intrathecal morphine has been used, and also that its use is consistent with a stable perioperative haemodynamic state [44]. After coronary artery bypass surgery, patients who had received morphine 0.5 mg intrathecally required significantly less sodium nitroprusside and fewer i.v. supplements of morphine; there was, however, no difference in pain score [190].

The dose of morphine used by this route has been decreasing gradually. Recently, doses of 0.1 mg and 0.25 mg have been shown to produce excellent and prolonged analgesia (18.6 and 27.7 h, respectively) after Caesarean section [1]. However, there is a lack of information on the optimum dose of intrathecal morphine. A comparison of 0.3, 1.0 and 2.5 mg found that the low dose was associated with an inconsistent duration of analgesia and irritating side effects [93]. The larger doses provided excellent analgesia, but also a high incidence of respiratory depression.

Diamorphine [16, 144] and buprenorphine [37] have also been used intrathecally with good effect. Pethidine is the only drug that has been used successfully intrathecally as the sole anaesthetic agent, for genito-urinary [130] and lower abdominal and lower limb surgery [172]. The doses were 0.1 mg kg^{-1} and 100 mg, respectively; the effects may have been related to the local anaesthetic properties of pethidine.

Specialist Applications

Obstetric analgesia

Although extradural local anaesthetics will abolish the pain of labour, their use is associated with a number of problems. They are relatively short acting and so require repeated injection or a continuous infusion; hypotension is an ever present risk and accidental i.v. or intrathecal injection can have major consequences. The possibility of producing prolonged analgesia with small doses of opioids was therefore exciting.

However, extradural morphine has proved to be disappointing. Husemeyer and colleagues [91] found 2 mg to be totally ineffective in relieving the pain of the first stage of labour. Others found that 2.0 and 5.0 mg did not produce satisfactory pain relief, whereas 7.5 mg did during the first, but not the second stage of labour [90]; this is approaching the systemic dose. Extradural fentanyl 150–200 μg produced excellent pain relief until the late first stage, but was inadequate during the latter part of the first stage and during the second, when pain was at its worst [38]. Addition of fentanyl 80 μg to the test dose of bupivacaine resulted in more rapid and complete analgesia compared with a control group [99]. Pethidine 50 mg alone did not produce as effective analgesia as pethidine with adrenaline [146, 147]. Alfentanil, however, was unsatisfactory [88].

Intrathecal administration has proved to be much more satisfactory in labour (fig. 1). Excellent analgesia, often lasting several hours, has been reported after morphine 0.5–2 mg given for the first stage of labour, although the effects were much less marked during the second stage [3, 15, 175]. The incidence of side effects, even though classified as "minor", was distressingly high [3]. It is possible to decrease these with naloxone without affecting the degree of analgesia [29], but this complicates what should be a simple technique. Despite the simplicity and efficacy of using intrathecal opioids in labour, Crawford [56] has warned that the potential for respiratory depression always exists and makes routine use of the technique in obstetrics difficult to accept. Apnoea has now been reported some 7 h after intrathecal morphine 1 mg given to a mother in labour [4].

In view of the high incidence of side effects, intrathecal morphine in labour would best be reserved for those situations in which it is essential to avoid the unwanted effects of local anaesthetics, particularly hypotension, for example in patients with congenital heart disease [5].

Paediatric use

There are few reports of the use of spinal opioids in children. Jones and colleagues [98] found that postoperative analgesia lasted more than 24 h in 22 of 56 children given intrathecal morphine before the surgical incision. Fifteen children required additional analgesia at 22 h, while in the remainder pain relief lasted approximately 13 h. The initial 27 children received a dose of 0.03 mg kg^{-1}, but six of these developed respiratory depression an average of 4.4 h after the morphine and required naloxone. The remaining children were given 0.02 mg kg^{-1} and three of these required naloxone to antagonize respiratory depression.

Extradural morphine behaves in a similar way

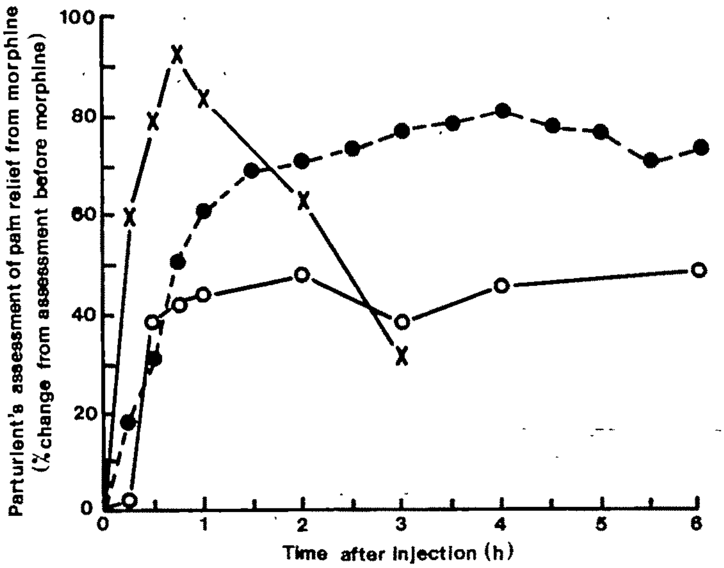

FIG. 1. Maternal pain relief (before delivery), after extradural administration of 0.5% bupivacaine 10 ml (×), extradural administration of morphine 7.5 mg (○) or intrathecal injection of morphine 0.5 mg and 1.0 mg (●). (Reproduced by kind permission of Dr T. K. Abboud and her colleagues [3] and the editor of the *British Journal of Anaesthesia*.)

as in adults. A dose of 50 µg kg^{-1} after abdominal or genito-urinary surgery showed an onset time of 30 min and an average duration of 19.5 h [11]. Complications were also similar, with incidences of pruritis of 20%, nausea and vomiting of 40% and urinary retention of 28%. The ventilatory response to carbon dioxide was depressed after surgery and before morphine, probably as a result of the residual effects of the anaesthetic, but remained low for 22 h, probably because of the extradural morphine. The pharmacokinetic parameters were similar to those in the adult, except for a shorter terminal half-life resulting from the greater total body clearance in children. Extradural sufentanil has also been shown to produce rapid, effective, but short lasting analgesia (mean 198 min) in children [20]. The complications were similar to morphine, but drowsiness was also reported in 67% of the children. The slope of the carbon dioxide response curve was significantly depressed for up to 60 min, which led the authors to recommend close monitoring for more than 1 h. About 50% less parenteral narcotic was given to children who received caudal morphine 0.07 mg kg^{-1} in 5 or 10 ml at the end of cardiac surgery [165]. The caudal morphine was effective after both thoracotomy and sternotomy, although increased sedation was common.

Other acute pain

Extradural morphine was an effective method of pain relief in patients with multiple fractured ribs [97, 119], but intrathecal morphine 1.0–2.0 mg did not provide adequate analgesia in 27% of such patients, and the incidence of complications was high [63]. Extradural methadone 4 mg given before operation facilitated mobilization and easier nursing in patients with proximal femoral fractures [138]. Extradural fentanyl was found to be efficacious, easy to use and a safe alternative to both general anaesthesia and conventional extradural analgesia in patients undergoing extracorporeal shock wave lithotripsy [141].

The pain of acute myocardial infarction has been relieved by both intrathecal [143] and extradural morphine [180]. In both instances pain relief was obtained where the i.m. and i.v. routes had failed. Morphine 2–3 mg given through thoracolumbar catheters on an outpatient basis once or twice a day resulted in a lessening of angina in seven patients who had already undergone coronary artery surgery and in whom other medical treatment was ineffective [49].

Spinally applied opioids are effective in a number of acute painful conditions and this is an area which would benefit from more intensive investigation.

PHARMACOKINETIC ASPECTS

A knowledge of the pharmacokinetic behaviour of spinally applied opioids will help in the understanding of the observed pharmacodynamic effects, but requires measurement of plasma and CSF concentrations. The major analgesic effect of extradural opioids depends on movement of the drug across the dura and into the spinal cord. Thus the more fat soluble drugs would be expected to cross the dura more rapidly, but a study using an isolated preparation of lumbar and cranial dura found that lipophilicity was apparently not an important factor because morphine and diamorphine had similar permeabilities [127]. There was a marked relationship between the permeability of the compounds tested and molecular weight with the exception of fentanyl, which crossed the dura faster than would be expected. The authors suggested that molecular shape may be the important factor and that, whereas most of the compounds they tested had a shape approximate to a sphere, fentanyl is an extended molecule. However, the conditions of the experiment were very artificial and the dura is not a lipid membrane.

Once in the CSF, the opioid has to diffuse into the spinal cord in the region of the dorsal horn of grey matter to exert its effect [204]. In animal experiments, cats were studied 1–3 h after intrathecal administration of carbon-14 labelled morphine. Radioactivity was limited mainly to the external 1–2 mm of the cord even at the longest time interval, while only minimal penetration was seen at the shortest. This would explain the long latency seen after morphine.

After extradural morphine, peak plasma concentrations were reached at approximately 15 min and the plasma curves were similar to those seen after i.m. injection [132, 135]. Morphine crossed the dura slowly, appearing in the CSF in 15 min with peak concentrations between 90 and 120 min [135, 179], when the concentrations were about 25 times those in plasma. The half-lives in plasma and CSF are very similar: 3.5–4 h [134, 135]. Disappearance of morphine from CSF is prolonged, 80 % still being present 4 h after injection and about 50 % at 12 h [179]. The CSF concentration 24 h after extradural morphine 6 mg was approximately 16 ng ml^{-1} [134]. However, the amount of morphine actually entering the CSF after extradural injection is small, Nordberg and colleagues [134] calculating the CSF bioavailability to be approximately 2.0 %, whereas Sjostrom and colleagues [179] found that the fraction crossing the dura was 3.6 %.

It might be expected that the larger the volume of the injectate containing the opioid the greater would be the absorption because of the more widespread distribution, but this has not proven to be the case. A volume of 10 or 20 ml did not influence CSF concentration of morphine [132]. Others found no difference in serum concentrations of morphine after 6 mg in 3 ml or in 30 ml, although analgesia lasted somewhat longer after the larger volume [173]. It has also been noted that increasing the volume of diluent for fentanyl 50 μg did not slow onset time and decrease the duration of effect as expected, but exactly the reverse [8]. Doubling the volume of injectate with the same mass of drug had no effect on the quality or duration of analgesia [149].

Diamorphine, the diacetyl derivative of morphine, is much more fat soluble and clinically has a more rapid onset and shorter duration of effect than morphine. In the blood stream it is rapidly deacetylated to morphine, but this occurs only very slowly in CSF. Thus an indication of its systemic absorption can be obtained by measuring the plasma concentration of morphine. Watson and colleagues [194] found that peak plasma concentrations after extradural diamorphine 5.5 mg occurred significantly faster, and were significantly higher, than after morphine 5.0 mg. They estimated the fraction of diamorphine crossing the dura to be 55 % that of morphine.

Pethidine is also more fat soluble than morphine and has a faster onset and shorter duration of action. Peak CSF concentrations occurred at 15–30 min, but the fraction crossing the dura was the same as for morphine [179]. It disappeared from the CSF about four times faster than morphine [179].

After intrathecal morphine 2.5 mg given before cardiopulmonary bypass, CSF concentrations decreased rapidly for 10 min and then reached a plateau at 10 μmol litre^{-1} [126]. After diamorphine 2.0 mg, the concentrations decreased rapidly initially and continued to decrease during the 25-min study period, thus indicating that diamorphine is removed more rapidly from the CSF, This conclusion was confirmed by the work of Kotob and colleagues [104], who measured plasma and CSF concentrations for 6 h after 1 mg of intrathecal morphine or diamorphine. After morphine, peak plasma concentrations were significantly lower, and peaked significantly later, than after diamorphine. The mean elimination half-life of diamorphine from CSF was 43 min compared with 73 min for morphine.

Apart from passing out of intervertebral foramina, there are three possible fates for drug injected into the extradural space, namely vascular absorption, dissolving in extradural fat or dural transfer. It is possible to influence the first of these by inclusion of a vasoconstrictor in the injectate. Adrenaline, however, did not influence plasma or CSF concentrations of morphine, or the duration of analgesia after extradural injection [136]. In contrast, addition of adrenaline to diamorphine significantly decreased plasma concentrations of morphine by decreasing systemic absorption by over 50%, and also prolonged the duration of analgesia [95].

The available pharmacokinetic data explain the pharmacodynamic effects of spinal opioids. They have demonstrated the slow dural transfer of morphine and its prolonged presence in the CSF, thus correlating with its slow onset and long duration of action, and high incidence of side effects. They have also demonstrated that the more fat soluble drugs enter the circulation more rapidly and also leave the CSF more rapidly than morphine; thus less is available for rostral spread in the CSF and side effects should be fewer.

COMPARISON OF TECHNIQUES

Intrathecal with Extradural

Nordberg [133] has commented that the extent to which the extradural route is preferred to the intrathecal is rather surprising. Apart from the fact that an intrathecal injection is technically easier, there are good arguments for considering it the more logical. The main determinant of spinal analgesia is the CSF concentration of the opioid. Direct intrathecal injection avoids the problem of systemic absorption and the possibility of the drug dissolving in the extradural fat, both of which compete with dural transfer of the drug. Peak CSF concentrations of morphine occur 1–2 h after extradural injection. The CSF bioavailability of extradural morphine is about 2.0% [134] and an intrathecal dose of 0.2 mg would produce CSF concentrations similar to those resulting from the injection of 10 mg to the extradural space. Furthermore, a single injection produces prolonged analgesia.

There have been no double-blind controlled trials comparing the two methods of administration. The intrathecal route has been reported as being superior to the extradural [16], but as the doses of the drugs (morphine 2.0 mg, diamorphine 0.5 mg) were the same by both routes, this is not surprising. A retrospective study [77] revealed that after thoracotomy there was no difference in the quality of analgesia between extradural and intrathecal morphine, but that this was of longer duration and achieved with a much smaller dose of drug after intrathecal injection.

The reason for anaesthetists preferring the extradural route is that the incidence of complications, both minor [3, 93] and major [60, 79, 87, 152], is much greater after intrathecal use.

Spinal Opioids Compared with Existing Techniques

Extradural and intrathecal injections require skill to perform, have a documented failure rate (particularly thoracic extradural) and may be associated with serious complications and even death. It is possible, with attention to detail, to produce adequate postoperative pain relief by much simpler methods using i.m. [12] or i.v. injection, or even regular sublingual administration [33]. In view of this, the risk:benefit ratio of spinal opioids must be carefully balanced and it is essential that this new technique be shown to offer significant advantages over existing methods of pain relief.

Many of the initial reports of spinal opioids were nothing short of spectacular, with claims of minimal doses of drug producing very prolonged analgesia and virtually no complications. Unfortunately, these reports failed to adhere to the basic principles of clinical evaluation of new techniques and it was impossible to eliminate bias from the observations. In order to obtain a valid comparison with conventional methods of analgesia a number of steps must be followed. First, there must be an acceptable method of evaluation of pain relief. This might involve subjective assessment on pain scales, a visual linear analogue, or a more objective method such as measurement of respiratory function when relevant to the surgery performed. The number of demands for additional analgesia from a patient controlled device is also acceptable, but the number of i.m. injections given at the discretion of a nurse is not; even in the best units, the latter would only give some indication as to the duration of analgesia, not its quality. Second, allocation to the two treatment groups must be randomized. Third, to eliminate bias, each patient must receive an extradural or intrathecal injection *and* each must receive either placebo or drug by the other route of administration. Fourth, again to eliminate bias, all medications must be given on a double-blind basis. Fifth, the groups must be comparable in terms of the origin and severity of the pain to be treated.

To perform such a trial is time consuming, administratively difficult and could also be questioned from an ethical point of view. It is also necessary to use equipotent doses of the drug, but information on relative potencies is not available when comparing spinal and systemic administration. For instance, there is a marked difference between the systemic and extradural potencies of pethidine and morphine [178]. Even the best controlled trials can be beset with problems. Thus in a cross-over trial comparing extradural pethidine 50 mg with 100 mg given i.m. and extradural bupivacaine after lower abdominal surgery, the former was shown to be superior [31]. However, the distribution of treatments was such that many more patients received extradural pethidine as their third and fourth treatments, and intensity of pain diminishes as time passes after surgery.

Jacobson and colleagues [94] found no significant difference in the quality of analgesia when diamorphine 0.1 mg kg^{-1} was compared by the extradural or i.m. routes, although duration of effect was longer in the former group. Extradural morphine 5 mg produced a longer period of analgesia than 10 mg given i.m., but otherwise there was no great difference between the two [40]. In grossly obese patients, there was no significant difference in the quality of analgesia produced by morphine 0.1 mg kg^{-1} i.m. or 4 mg given extradurally, but morphine consumption was much greater after i.m. injection, being a mean of 1.8 mg h^{-1} over 36 h compared with 0.26 mg h^{-1} [156]. Using a patient controlled analgesia system for i.v. and extradural fentanyl, no significant difference in overall pain relief was found by subjective or objective measurements [74].

Other workers have found the extradural route superior. Extradural diamorphine was found to produce more prolonged and intense analgesia than the same dose given i.m. [116]. Malins and colleagues [120] found thoracic extradural diamorphine 5 mg superior to the i.m. route and could not agree with Jacobson and colleagues [94] that i.m. diamorphine could exert an effect for so long after thoracotomy. Fentanyl 200 μg given into the extradural space produced more effective analgesia than 200 μg i.m., although this effect was apparent only for 60 min [112].

TABLE IV. *Incidence of "minor" side effects after extradural and intrathecal morphine*

	Extradural [202]	Intrathecal [3]
Pruritis	41 %	80 %
Nausea	48 %	53 %
Vomiting	30 %	
Urinary retention	34 %	43 %

There is no conclusive evidence that opioids injected extradurally or intrathecally provide analgesia superior to that produced with other routes of administration. An undisputed advantage, however, is their ability to produce more prolonged analgesia at much smaller doses. Extradural morphine produces long lasting analgesia with doses that are only 20–40 % of the normal i.v. dose; 8 % of such doses are effective when given intrathecally [59]. Thus patients could be expected to be less drowsy, more co-operative and more mobile, with all the attendant advantages.

SIDE EFFECTS

Acceptance of a new technique depends not only on its efficacy, but also on the nature and incidence of side effects. The latter occur frequently after extradural and intrathecal opioids, and although many are regarded as being "minor", they can nevertheless be very annoying to the patient. Typical incidences are shown in table IV, although the frequencies of those mentioned vary from zero to almost 100 % in individual reports.

Minor Sequelae

Nausea and vomiting

This side effect cannot be divorced from the use of opioids. In volunteers, Bromage and colleagues [28] observed nausea and vomiting about 6 h after extradural morphine in all subjects. In general, the incidence appears to be greater after intrathecal injection, but it should be remembered that there is a 30 % incidence after parenteral use of opioids [54].

Pruritis

The reported incidence of this annoying side effect varies considerably and has been reported as occurring in 100 % of volunteers given extradural morphine 10 mg [27]. In one series, up to 67 % of patients developed pruritis after morphine, the incidence being unrelated to the dose [121]. This contrasts with the report of Lanz, Kehrberger and Theiss [106], who found that the incidence of pruritis after extradural morphine increased from 17 % after 1.0 mg to 56 % after 5 mg. Pruritis on the face and trunk began 3–5 h after intrathecal morphine 0.5–1.0 mg and lasted for up to 30 h [3]. It has also been reported after extradural fentanyl and diamorphine, but there are virtually no data comparing the drugs.

The itching is not confined to the segmental area of action of the opioid, but also occurs around the head and neck. The mechanism is not known, but it is unlikely to be the result of histamine release because there is no other evidence of such a reaction and it occurs with fentanyl, which does not release histamine. Korsch and colleagues [103] did not find increased plasma histamine concentrations in patients who complained of pruritis after extradural morphine 5 mg, and the concentrations during the maximum period of itching did not differ from those who had received i.m. pethidine. Although there is no generalized histamine release, this does not rule out local tissue release of histamine. The overall incidence after extradural morphine is about 10 % and it is severe in about 1 % [152]. After extradural pethidine, Brownridge [30] noted that about 33 % of 2000 patients complained of itching, but usually only on direct questioning, and that the symptom usually diminished with subsequent doses. In only one of these patients was the pruritis severe. The original belief that the pruritis was caused by the preservative in the injectate has been discounted. The pruritis can be antagonized with naloxone [29].

Urinary retention

This has been described as the most troublesome complication of extradural opioids [152], and an incidence of 90 % or more can be expected in young males receiving extradural morphine 10 mg [26]. In the reported clinical series the incidence varies widely. Torda and Pybus [186] noted that only one of 24 patients required catheterization, but in other series frequencies of 22 % [158] and 39 % [108] have been reported. Urinary retention occurred in 79 % of patients undergoing ano–rectal surgery [86].

Rawal and colleagues [154] studied the urodynamic effects of extradural morphine 2, 4 and 10 mg and of morphine 10 mg i.m. They found that, irrespective of dose, extradural morphine resulted in a marked relaxation of the detrusor muscle shortly after injection, with a corresponding increase in maximal bladder capacity leading to urinary retention. This lasted an average of 14–16 h. Only minimal effects were seen after i.m. or i.v. injection. The duration of effect was not dose related. The rapid onset and the absence of effects after parenteral administration favour a spinal action and may result from interference with sacral parasympathetic outflow. There may possibly be opioid receptors in the urinary bladder. All these effects were antagonized promptly by naloxone 0.8 mg i.v.

All these "minor" side effects have also been reported in children, with similar frequency [11, 20]. They also occur more often after intrathecal than after extradural injection (table IV).

Serious Sequelae

Neurological damage

The possibility of permanent neurological damage after any extradural or intrathecal procedure is always cause for concern. Permanent neurological sequelae have not been a problem, although one case of meningitis has been reported after long-term treatment [9].

Preparations containing preservatives should not be used, as some of these are known to be neurotoxic, for example chlorocresol. Problems have occurred in a patient receiving long term extradural morphine therapy for intractable pain [71]. Originally a preservative free preparation was used, but this was changed to a generic product for cost reasons. This caused a burning pain on injection, with less satisfactory analgesia. An extradurogram showed non-specific areas of flow restriction. The generic formulation contained phenol 2.5 mg and formaldehyde 2.8 mg with morphine 15 mg and it was calculated that the patient had received phenol 30 mg and formaldehyde 33.6 mg during therapy with this preparation. Satisfactory pain relief was reinstated after return to preservative free morphine.

It is unlikely that any of the opioids which have been used extradurally or intrathecally cause neurological damage.

Respiratory depression

The specific advantage that it was most hoped would be gained from the use of spinally applied opioids, namely absence of respiratory depression, has not been obtained. The literature now abounds with case reports of this complication, the most sinister aspect of which is its delayed appearance. After intrathecal opioids, respiratory depression develops 6–11 h after administration and may last for as long as 23 h [60]. After extradural opioids, respiratory depression can occur within 1 h, and in just a few minutes with the more fat soluble drugs [23, 192], although most instances have been delayed for 4–6 h. A delay of 16.5 h has been reported [202]. Morphine is almost invariably the drug involved.

Studies in both volunteers and patients have consistently shown significant and prolonged respiratory depression after extradural morphine. Maximum depression of the carbon dioxide response curve was found between 6 and 10 h after extradural morphine 10 mg in volunteers and there was still evidence of depression 22 h after injection [36]. Similar results were found by Knill, Clement and Thompson [102] who found that the end-tidal carbon dioxide concentration was still increased and the slope of the carbon dioxide response curve was still slightly depressed 24 h after extradural morphine 3.5 mg. Measurement of airway occlusion pressure responses to carbon dioxide were depressed after extradural morphine 10 mg in young patients after abdominal surgery, indicating a decreased respiratory drive, but there was a high degree of individual variability in the magnitude and course of this effect [64]. Rawal and Wattwil [159] found a dose related depression of the response to carbon dioxide, while Madsen and colleagues [118] recorded a significantly increased Pa_{CO_2} 20 h after extradural morphine 8 mg. Prolonged ventilatory depression has also been reported in children [11].

Maximum depression of minute ventilation occurred 1–2 h after injection of extradural morphine 0.1 mg kg^{-1} in patients with chronic back pain [100]. The authors proposed that this was a result of vascular absorption of the drug and distribution to the brain, but they also found a late depression of the response at 8 h, which corresponded with the maximal rise in the segmental level of analgesia and loss of skin temperature discrimination. There was considerable variation in the magnitude of this late displacement.

A respiratory inductance plethysmograph has been used to study respiratory pattern after extradural or i.v. morphine given after thoracotomy [171]. Morphine 5 mg was given extradurally approximately 1 h before the end of surgery and further 5-mg doses were given when necessary. The results were compared with those for i.v. morphine given in a double-blind manner, and are shown in figure 2. Periods of hypopnoea/apnoea or slow rates of ventilation were seen in six of eight patients given extradural morphine, but in only one of the i.v. group. The authors commented that the alterations in respiratory pattern were subtle and insidious in onset and unpredictable in duration, and the fact that no patient required naloxone or artificial ventilation should not detract from the inherent dangers of postoperative use of extradural morphine. They stressed that hourly monitoring of ventilatory rate could be quite misleading.

The explanation of the delayed respiratory depression lies in the pharmacokinetic properties of morphine. Being poorly lipid soluble, it enters the spinal cord slowly and its disappearance from the CSF is prolonged [179]. It therefore remains in the CSF and slowly migrates cephalad. Observations on the circulation of CSF have shown that it takes 1–2 h to reach the cisterna magna from the lumbar region and 4–8 h to pass through the foramina of Luschka and Magendie to the fourth ventricle [62]. Experimental work in primates found that intrathecal morphine was maximally concentrated in the medulla at 6 h [85]. Any factors that accelerate the movement of morphine in the CSF will result in a more rapid appearance of, and perhaps a more profound, respiratory depression [100]. These latter authors reported a patient who experienced coughing 3 h after extradural morphine 0.1 mg kg^{-1}, which resulted in a rapid rise in segmental analgesia, to include the mandibular and maxillary divisions of the trigeminal nerve by 4 h. This was accompanied by severe respiratory depression.

Incidence

The true incidence of respiratory depression will be known only when the results of large series, of which there have been very few, are available. The largest numbers come from two reports from Sweden (table V). In the first of these [87], respiratory depression occurred after

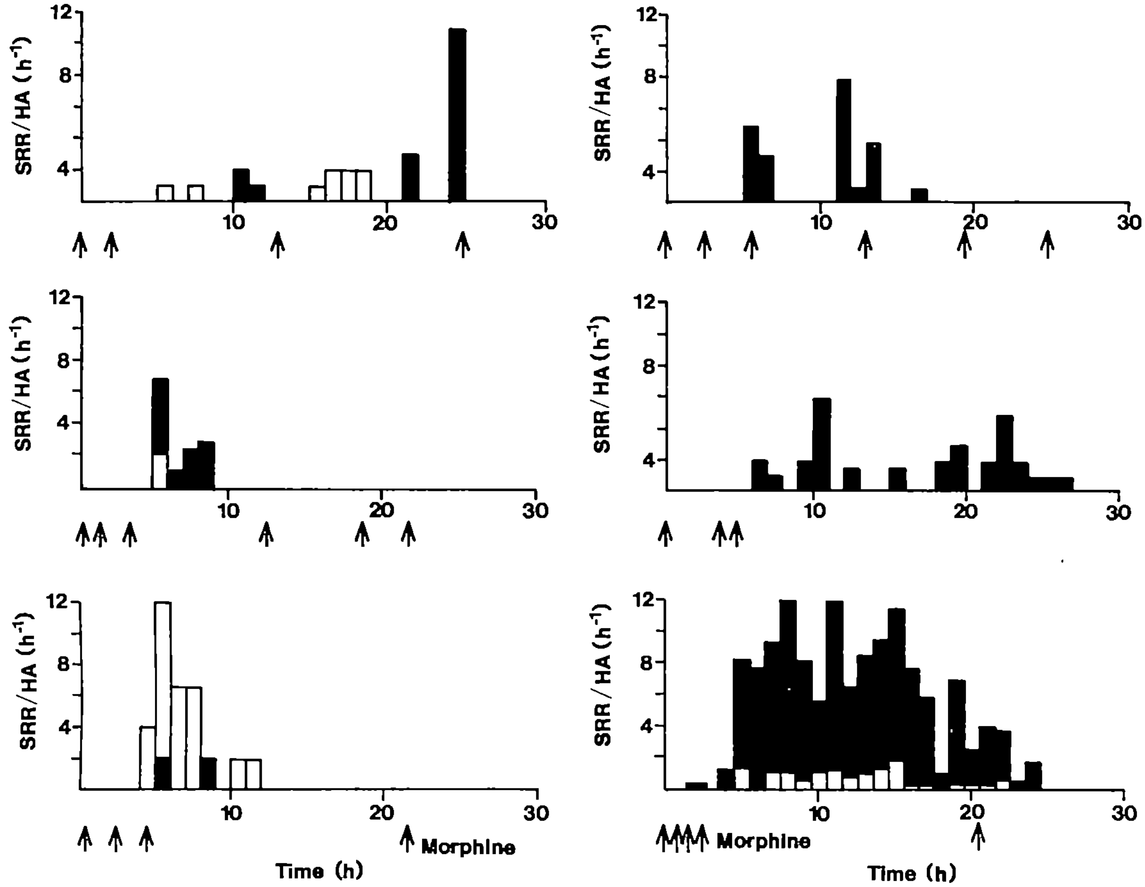

FIG. 2. □ = Number of instances per hour of a slow respiratory rate (SRR), defined as less than 10 b.p.m. for at least 5 min; ■ = number of instances per hour of hypopnoea/apnoea (HA) lasting for 15 s or longer; six of eight patients given lumbar extradural morphine after thoracotomy. Arrows indicate time of administration of extradural morphine 5 mg in normal saline 20 ml, the first dose being given during operation. There is considerable individual variation in dose requirements and in three of the patients demands for analgesia occurred at the same time as a slow ventilatory rate or hypopnoea/apnoea. (Reproduced by kind permission of Dr A. N. Sandler and his colleagues [171] and the editor of the *Canadian Anaesthetists Society Journal*.)

TABLE V. *Incidence of respiratory depression following extradural morphine*

n	Dose (mg)	Number	Incidence	Reference
6–9000	2–4	23	1:260–391 (0.25–0.4%)	[87]
11000	4	13	1:1100 (0.09%)	[153]
1085	4–6	10	1:109 (0.9%)	[181]
623	4–5	4	1:156 (0.6%)	[160]
128	5	4	1:32 (3.1%)	[202]

extradural morphine 2.0–4.0 mg in 0.25–0.4% of patients. In the second [153], morphine (usually 4 mg) was used in 96% of patients and the incidence of respiratory depression decreased to 0.09%. Both reports noted a much higher frequency of respiratory depression after intrathecal morphine.

The findings of these Swedish workers are not in accord with those of others who use morphine. Thus respiratory depression occurred in four of

TABLE VI. *Respiratory depression after extradural opioids other than morphine*

Drug	Dose	Time of occurrence	Reference
Diamorphine	2–10 mg	20 min–4.5 h	[53, 137, 194]
Pethidine	50–100 mg	5–30 min	[32, 174]
Methadone	4–6 mg	20 min–4 h	[196, 197]
Hydromorphone	1 mg	4.5 h	[203]
Sufentanil	50 µg	5–15 min	[23, 192]
Fentanyl	100 µg	30 min, 4 h	[142, 199]

623 patients (1 in 156, 0.6%) reported by Ready and colleagues [160] and four of 128 (1 in 32, 3.1%) in a Canadian multicentre trial [202]. In another large series [181], the incidence of respiratory depression was 0.9% in patients who received morphine 4–6 mg with a tendency for more frequent occurrence after thoracic extradural injection. Apart from isolated case reports, many studies investigating the analgesic effects of extradural and intrathecal morphine, and containing relatively few patients, have reported instances of respiratory depression, occasionally with alarming frequency. Thus three of six patients given morphine 1.0 mg intrathecally developed profound, delayed respiratory depression [60]. After morphine 5 mg by the thoracic route, eight of 30 patients gradually lost consciousness with respiratory depression 30–73 min after the injection, the general anaesthetic having contained no opioid analgesic [72].

It should be noted that the Swedish studies were retrospective, which have several problems of data retrieval. Also, many of the patients were being treated for chronic pain conditions and these patients are known to be resistant to the respiratory depressant effects of opioids [54].

Respiratory depression can also follow use of the more fat soluble opioids (table VI). When occurring soon after injection it can be ascribed to systemic absorption. Scott and McLure [174] reported two patients who developed severe depression within 30 min of extradural pethidine 50 mg, while Brownridge, Wrobel and Watt-Smith [32] reported a patient who became increasingly drowsy with gasping ventilation after pethidine 50 mg given into a catheter that was accidentally placed intrathecally. It is pertinent to note with regard to this case that the nurse had actually left the patient's room, but fortunately the husband drew attention to the problem. Extradural sufentanil has been followed within a few minutes by respiratory depression [23, 192]. Three of 12 patients given extradural diamorphine 5.5 mg had ventilatory rates of less than 8 b.p.m. between 20 and 90 min later [194], while all patients given 10 mg into the thoracic space had evidence of respiratory depression some 2 h later [137].

There may possibly be an association between the appearance of respiratory depression after extradural administration which has been complicated by previous dural puncture [53, 196]. Radiological evidence exists of injectate into the extradural space passing through a previous accidental dural puncture hole into the subarachnoid space [110].

More sinister delayed respiratory depression can also occur. Extradural diamorphine 3 mg resulted in apnoea at 4.5 h in a patient who had also had a spinal anaesthetic [53]. Respiratory depression occurred 4 h after lumbar extradural methadone given after thoracic surgery [197]. Hydromorphone 1.0 mg, which is much more fat soluble than morphine, caused apnoea 4.5 h later in a patient who had not received any other opioid in the previous 10 h [203].

Theoretically, respiratory depression should occur less frequently with the more fat soluble opioids as they will enter the spinal cord more rapidly and will not remain in the CSF. There are far fewer cases reported, but the frequency of use of these agents compared with morphine is not known. Few experimental studies have been performed. Diamorphine 5 mg either i.m. or into the thoracic extradural space depressed respiration maximally within 30 min of injection and, although statistically significant, its clinical importance was slight [120]. Ahuja and Strunin [6] investigated the respiratory effects of a bolus injection of fentanyl 1.5 $\mu g\ kg^{-1}$ followed by a continuous infusion into the thoracic extradural space. The bolus injection resulted in a significant decrease in rate of ventilation and a non-significant increase in end-tidal carbon dioxide concentration within minutes, which was similar to the findings of others [112]. The changes were accentuated by prior parenteral administration of morphine. A continuous infusion of fentanyl 50–100 $\mu g\ h^{-1}$ commenced 1 h after the bolus injection and continued for 18 h had no further effect on the end-tidal carbon dioxide concentration or ventilatory rate, despite a gradually increasing plasma concentration of fentanyl.

Molke-Jensen and colleagues [123] were disappointed to find that the very fat soluble buprenorphine in an extradural dose of 0.15 mg produced prolonged and biphasic depression of the carbon dioxide response, with respiratory depression being significant between 2 and 4 h and again at 8–10 h. No clinical reports of respiratory depression after the drug have yet been reported. The mixed agonist–antagonist butorphanol 2–4 mg given extradurally depressed the ventilatory response to carbon dioxide for 12 h [2].

Thus all the narcotic analgesics have the propensity to produce respiratory depression, but there is no doubt that it is more common after morphine. Fentanyl may be the least problematic, although the frequency of its use is not known. Profound central nervous system and respiratory depression has followed just over 1 h after 100 μg given extradurally, but the patient had also received i.v. midazolam, droperidol and nalbuphine to counteract pruritis [199]. An infusion of naloxone was necessary to maintain respiration. Respiratory depression has been reported 4 h after fentanyl 100 μg with adrenaline, the definition of respiratory depression being a rate of ventilation less than 10 b.p.m. or a venous carbon dioxide partial pressure more than 1.33 kPa greater than control [142]. The rate of ventilation in this patient was 16 and the venous $P\text{CO}_2$ 1.47 kPa greater than control. This occurred in one of two patients given this dose of fentanyl and hardly justifies the claim of a 50% incidence of respiratory depression with this drug [152].

Predisposing factors

The factors that may predispose to the development of respiratory depression are shown in table VII. Most patients are elderly, 77% in the recent nationwide survey in Sweden being older than 65 yr. It is in these elderly patients, who frequently have concomitant cardiopulmonary disease, that good analgesia with minimal central depression is so often required. Nevertheless, profound respiratory depression can occur in the young [60, 203]. The water soluble drug morphine has been most frequently implicated, although it does occur with the more lipophilic drugs (table V).

TABLE VII. *Factors predisposing to the development of respiratory depression [54]*

Advanced age.
Use of water soluble opioids.
Concomitant use of parenteral opioids or other central nervous system depressants.
Lack of tolerance to opioids.
Increased intrathoracic pressure.
Intrathecal opioids.
Large doses.
Thoracic extradural opioids.

The residual effects of other central depressants are frequently quoted as being contributory to the respiratory depression produced by spinal opioids. Severe respiratory depression, resistant to naloxone, but antagonized with physostigmine, has been reported in a patient who received droperidol 1.25 mg i.v. for nausea after delivery, followed later by extradural hydromorphone 1.25 mg [50]. Lack of tolerance to opioids is another important factor and there does not appear to be a problem, even when very large doses are given extradurally to patients with intractable pain who have usually received large doses of a variety of drugs for some time [9]. The respiratory depressant effects of extradural morphine can be seen 16 h or more after administration [36] and further depressant drugs, by any route, at this time may result in significant respiratory depression.

Increased intrathoracic pressures, caused by artificial ventilation, coughing or the grunting respiration associated with pain may serve to accelerate passage of drug containing CSF cephalad. This is well illustrated in the case reported by Kafer and her colleagues [100]. The incidence is more common after intrathecal opioids [87, 153] and, although it has been reported after extradural administration after accidental dural puncture [53, 196], the number of such cases is too few to draw any firm conclusions. The large doses of morphine (10 mg) that may be required to produce satisfactory analgesia after upper abdominal surgery are associated with a higher incidence of respiratory depression than 2–4 mg [159]. It is also more common after intrathecal doses greater than 1 mg [79, 93]. The thoracic extradural approach also is associated with a higher reported incidence [87, 181].

A wide spectrum of factors are involved in the development of this complication, so much so that the most predictable thing that can be said about its appearance is that it is unpredictable. This has important implications for the management of patients who have received spinal opioids.

Prevention

It has been suggested that patients receiving spinal opioids should be nursed in the semi-sitting position, in the hope of preventing respiratory depression. It has been suggested that intrathecal opioids should be used in hyperbaric solution [170], but supporting evidence for these views have not been forthcoming. Respiratory depression has followed hyperbaric morphine 1.0 mg in a patient kept in the head-up position [4]. McCaughey and Graham [113] found a consistent pattern of respiratory depression after extradural morphine 2 mg in patients kept supine. In the sitting position the same degree of respiratory depression was not observed, although there was considerable individual variation. Others have found that the 45° elevated position offered no protection with regard to the incidence or degree of respiratory depression after lumbar extradural morphine 4 mg [124]. The head down position should be avoided. Severe respiratory depression has occurred after only 0.4 mg of hyperbaric morphine given intrathecally in such circumstance [80].

Naloxone antagonizes all the unwanted effects of spinal opioids, although repeated doses may be necessary to maintain adequate ventilation. Analgesia is not usually affected, and this has led to attempts to reduce the incidence of side effects by concomitant administration of naloxone. Thind, Wells and Wilkes [184] found that naloxone 2 mg given by infusion over 12 h after extradural morphine 4 mg did not affect analgesia and reduced the severity, but not the incidence of side effects. There was no respiratory depression. Rawal and colleagues [155] used 5 and 10 $\mu g\ kg^{-1}\ h^{-1}$ after extradural morphine 4 mg and found that the larger dose decreased the duration of analagesia by about 25%. The naloxone also reduced the incidence of side effects and a dose related stimulatory effect on ventilation was seen.

These findings are contrary to those of Gowan and colleagues [84], who used three bolus doses and infusion rates of naloxone in patients given extradural morphine 0.1 $mg\ kg^{-1}$. There was a trend towards decreased analgesia with all three rates of infusion of naloxone and side effects occurred in all groups. They concluded that a naloxone infusion was not an appropriate technique for reducing side effects while maintaining analgesia after extradural morphine.

The partial opioid agonist nalbuphine also has been used to prevent respiratory depression [68]. A bolus dose of 0.2 mg followed by an infusion of 0.05 $mg\ kg^{-1}\ h^{-1}$ resulted in lower arterial carbon dioxide tensions than in a control group. Naloxone was required in the latter patients. The results of giving a partial agonist in the presence of an agonist may be additive or antagonistic, depending on the relative concentrations of two drugs [35], and it would be wiser to avoid such a drug combination.

FEASIBILITY OF USE OF SPINAL OPIOIDS FOR POSTOPERATIVE PAIN RELIEF

Intrathecal and extradural opioids produce excellent analgesia with much smaller doses of drug than is achieved via other routes. There is therefore less central depression and greater patient mobility and co-operation, with all the attendant benefits. A major advantage over extradural local anaesthetics is the lack of autonomic block and absence of hypotension. However, there is no doubt that their use is associated with a high incidence of complications, the most sinister of which is delayed respiratory depression.

The proposition of a single injection given at the time of surgery and providing long lasting analgesia is very attractive. A single intrathecal injection of morphine has been shown to be beneficial to patients undergoing abdominal aortic and coronary artery surgery. Significantly less parenteral analgesia is required after operation, the time spent in the intensive care unit is shortened [92] and significantly less hypotensive agents are required after cardiac surgery [190]. However, these types of patient are nursed in an intensive care unit and their lungs are usually ventilated artificially after operation. It would certainly be feasible to perform a single intrathecal injection for the majority of patients undergoing surgery, but repeat administration in the postoperative period would not be possible, there being few anaesthetists prepared to maintain a catheter in the subarachnoid space for several days. Performing an extradural injection is technically more difficult, is more time consuming and would not be a feasible proposition for as many patients. An extradural injection does have the advantage that catheter techniques are routinely practised, so that top up doses or continuous infusions are perfectly feasible. The incidence of complications is also lower after extradural opioids than intrathecal.

The biggest constraint on the use of spinal opioids is the nature and incidence of the associated complications. Pruritis, nausea and vomiting and urinary retention are common. The last of these is probably the most troublesome complication and must be taken into account when considering the technique for postoperative analgesia in the majority of patients who will not routinely have urinary catheters. However, the most serious problem is respiratory depression. Although more common after morphine, it does occur after other drugs and it is the unpredictability of its appearance that makes it so dangerous. Large comparative series have not been performed to indicate the frequency of occurrence with the different opioids.

Because of the problem of respiratory depression, the majority of workers recommend that these patients be kept in areas where there is a higher degree of surveillance than can be provided on an ordinary ward, and for up to 24 h after the last injection, certainly with morphine. Some form of respiratory monitoring is mandatory and probably most easily provided by the constant supervision of the nursing staff. Respiratory inductance plethysmography is not practical as a routine, and although apnoea alarms have been used [7], apnoea is the very problem that it is hoped to prevent. End-tidal carbon dioxide measurements can be valuable, while transcutaneous carbon dioxide electrodes still await critical analysis in a large series of patients. Pulse oximetry may also prove useful, but choosing the correct saturation below which intervention becomes necessary will depend on the individual patient. Respiratory depression usually comes on gradually, often indicated by a slowing of the rate of ventilation [181], and it is the trend indicated by the respiratory monitoring equipment that must be taken into account. Hourly monitoring of ventilatory rate is totally unacceptable. Use of continuous infusions of naloxone, although successful in reducing the severity of complications (but possibly also analgesic efficacy [84]), adds to the complexity of the procedure and mitigates against widespread use of the method.

In a nationwide survey in Sweden [153], it was reported that 33% of anaesthetic departments kept patients under close surveillance in an intensive care unit for 12–24 h after extradural morphine, 40% kept the patients under close surveillance for up to 12 h, and 18% returned the patients to an ordinary ward with no special observations. The incidence of respiratory depression in this survey was 0.09%, which is considerably lower than that reported by others with reasonably large series (table VI).

Recently, the development of an Acute Pain Service for the management of postoperative pain has been described. This allows use of patient controlled analgesia and extradural opioids in general wards as well as in areas of close surveillance [160]. Others have also described their experiences of using extradural opioids on general surgical and medical wards [34]. Ready and colleagues [160] stressed both that the service must be available on a 24-h basis, and the importance of a joint educational programme with the nursing staff. Standard procedures are issued, the nurses give the opioid (usually morphine) through the extradural catheter and have instructions on the treatment of complications. Criteria are laid down for the use of mechanical respiratory monitors, and for the circumstances in which they are not to be used. Both groups require naloxone to be immediately available.

Bursch and Stedman [34] have used this approach since 1984. They analysed retrospectively data from 125 patients and reported a low incidence of complications and no respiratory depression. Because the analysis was retrospective, they were unable to comment on the quality of analgesia. Ready and colleagues [160] reported that, after 18 months of operation, their service continues to grow and is popular with patients and surgeons. Extradurals have been used in 623 patients. Delayed respiratory depression occurred in four, all of whom were high risk patients who had undergone prolonged surgery and who were being cared for in an intensive care unit.

The policy of how and where to manage patients who are in receipt of spinal opioids must rest with individual anaesthetists and their departments. The programmes mentioned above are time consuming and require much manpower. It is difficult to see, given the facilities that exist in the U.K. at the moment and the commitments of nursing and medical staff, how such patients can be safely managed on an ordinary ward. The spectrum of occurrence of respiratory depression after extradural opioids is wide [203] and close surveillance is necessary for up to 24 h after administration. It is therefore difficult to justify returning these patients directly to an ordinary ward.

THE FUTURE

The introduction of spinal opioids has been an exciting and significant advance in the management of acute and chronic pain. The incidence of side effects, however, is high. Morphine is still the drug most commonly used worldwide, but the more fat soluble opioids are more popular in the U.K., although exact figures are not available. The search will continue for drugs with a more specific analgesic action at cord level, in the hope of removing the possibility of respiratory depression. Midazolam has been used extradurally [163] and intrathecally [83] and is effective in relieving somatic, but not visceral pain. Perhaps the analgesic actions of benzodiazepines can be developed without associated central effects.

Endogenous peptides have been used and prolonged analgesia has been reported after intrathecal β-endorphin [140]. An infusion of somatostatin after a 250-μg bolus provided complete analgesia after surgery and was not influenced by the administration of naloxone [46]. Modification of endogenous peptides might be possible and result in compounds with long lasting analgesic properties. Calcitonin has produced prolonged analgesia when injected intrathecally in patients with intractable pain [75] and was associated with significantly less postoperative pain when given together with lignocaine intrathecally for spinal analgesia [122]. The manufacturers of salmon calcitonin, however, have warned of its possible serious effects when used in this way [176]. For long term use in patients with intractable pain, drug combinations with the α_2-agonist clonidine or the synthetic opioid D-ala, D-leu-enkephalin (DADL) may help in those developing tolerance to opioids [52]. Droperidol has been used extradurally for this purpose, with benefit [13].

The future will also see more use of patient controlled analgesia given by the extradural route and the development of sophisticated infusion pumps for long term self-administration of opioids. Above all, what are needed are extensive, controlled, comparative trials to identify the most suitable drug for use in acute pain and the development of guidelines so that the technique can be extended to the majority of patients undergoing surgery.

RATIONAL USE OF EXTRADURAL AND INTRATHECAL OPIOIDS

The pharmacokinetic and pharmacodynamic effects of spinal opioids have been extensively investigated, but more work is necessary before the chapter can be finally closed on this new technique of analgesia. From the knowledge that exists at the moment, it is possible to suggest recommendations for their logical use in the management of acute pain.

Choice of drug. Morphine has been the most widely used and studied drug and, although its use has been defended [152], the incidence of complications are such that its routine use is difficult to accept. The lipophilic drugs are a much more logical choice, but large trials are necessary to identify the drug of choice.

Choice of dose. There is a wide variation in individual susceptibility to opioids and consequently in dose requirements. It is not logical to give a fixed dose to everyone, as has been done for many years with i.m. opioids with totally inadequate results. The dose should be titrated against the patient's needs and more use should be made of patient controlled analgesia. It is possible, however, to achieve adequate analgesia more easily with spinal opioids by giving a fixed dose of drug, but this does not allow for the patient whose needs are greater than average.

Choice of route of administration. Although it is more logical to use the intrathecal route, the logistical problems of giving repeat injections and in particular the high incidence of complications, do not make this the route of choice. Arguments have been made for routinely using the lumbar extradural route even after upper abdominal and thoracic surgery. Adequate analgesia does occur with morphine, and the incidence of respiratory depression is probably lower, but it is slow in onset, which might result in repeated doses being given in belief that the original dose was too small to be effective. With the lipophilic opioids, theoretical considerations would suggest that they should be given at the appropriate spinal level. Studies are required to confirm or refute this hypothesis.

Precautions and surveillance. Because of the complications, the degree of surveillance that is required cannot be provided on an ordinary ward. At the moment, close observation is recommended for 24 h, especially after morphine, although this period might safely be shortened for other drugs once information becomes available. It is imperative that nursing staff and resident medical staff be educated in their use, are instructed on the treatment of complications and are able to recognize the circumstances when urgent administration of naloxone is required.

Extradural and intrathecal opioids have been widely accepted by anaesthetists and have proved a valuable asset in the management of all types of pain. It would be a pity if one publicized disaster were to set back the technique by 20 years.

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Br. J. Anaesth. (1989), **63**, 189–195

SURGICAL STRESS: THE ROLE OF PAIN AND ANALGESIA

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The endocrine, metabolic and inflammatory responses to injury and infection are composed of a variety of physiological changes often grouped together and called the surgical stress response. Over the past few decades, detailed knowledge has accumulated on this response and has allowed consideration and development of therapeutic manoeuvres designed to assist or manipulate the patient's response to a surgical operation in order to improve postoperative morbidity.

Since relief of postoperative pain is supposed to be a prerequisite for improved postoperative outcome, this paper summarizes the effects on the surgical stress response of the available techniques. A short review of the clinical implications of postoperative pain relief will also be given. It is not intended to give a complete bibliography of this vast topic, but primarily to bring recent findings into balance with previous data. The reader is therefore referred to recent reviews of the surgical stress response, including release mechanisms and modifying factors [7,13, 14,16,17,25].

RELEASE MECHANISMS OF THE SURGICAL STRESS RESPONSE

Although the exact nature and relative importance of the various signals that may initiate, amplify, sustain and complete the stress response remain to be settled, recent studies have shed more light on the relative roles of afferent neural and humoral stimuli.

The nociceptive signal to the central nervous system is transmitted from the site of surgery primarily by small myelinated (A-delta) and unmyelinated (C) sensory afferent fibres [27,45]. Recent studies with regional anaesthesia producing total pain relief (which was assumed to include block of these fibres) suggest that fast conducting fibres may also be involved in the initial endocrine and metabolic response [14,16]. The relative roles of somatosensory and sympathetic afferents has not been specifically addressed, because the available blocking techniques are inadequate and non-specific. However, somatosensory and sympathetic afferents are probably more important in releasing the response than are vagal afferents [14,16]. The mechanism that sustains the response after injury has not been settled either, but functional changes within the peripheral and central nervous system leading to hypersensitivity in the response to nociceptive stimuli [41] may be of importance.

Although the neural stimulus is a major release mechanism for the surgical stress response, various humoral factors contribute, especially during major procedures and infection. The nature of the substances released at the site of trauma and from macrophages has been studied extensively during recent years, but a clear picture has not yet emerged. Of these, macrophage-derived peptides like interleukins and tumour necrosis factor seem to be most important in releasing various components of the stress response [16,22,25]. Although neural and humoral factors may in themselves be responsible for several aspects of the response, both inflammatory and endocrine (predominantly neurally mediated) factors must be activated to produce the full response.

MODIFYING EFFECT OF POSTOPERATIVE PAIN RELIEF

The various techniques available to provide pain relief in surgical patients and thereby eventually modify the surgical stress response are shown in figure 1.

Antagonists of peripheral mediators of pain

Injury leads to release of several endogenous algesic substances (histamine, serotonin, prostaglandins, leukotrienes, substance P, kinins *etc.*) which may facilitate the afferent nociceptive

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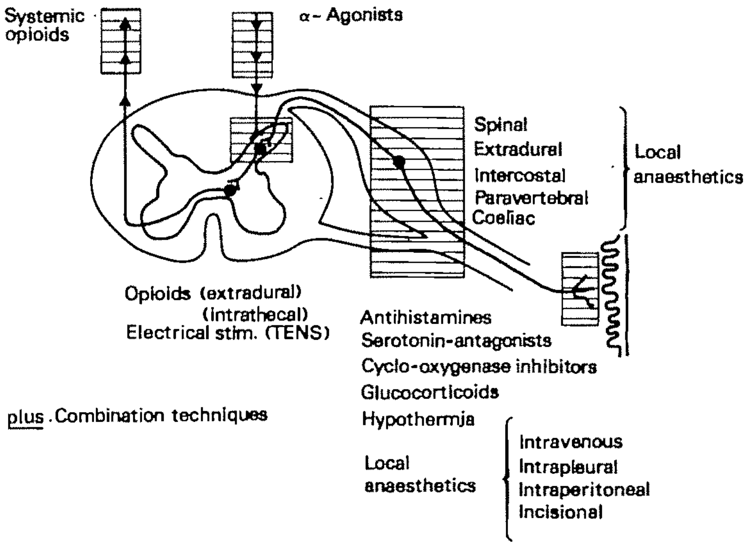

FIG. 1. Postoperative analgesic techniques which may alter the surgical stress response.

neural signal [27,45]. The analgesic effect of treatment with antihistamines or serotonin antagonists has not been settled, but is probably unimportant clinically. Furthermore, the metabolic effect of such an intervention is also negligible with regard to nitrogen turnover [38], temperature, acute phase and leucocytic responses [31].

The analgesic effect of cyclo-oxygenase inhibitors (indomethacin, ibuprofen *etc.*) is moderate [15,32], but the metabolic modification produced by these compounds is interesting because various inflammatory and cardiovascular responses may be attenuated. Thus after endotoxin, ibuprofen decreased pyrexia, tachycardia, increased metabolic rate and stress hormone release, while leucocytosis and acute phase protein changes were unaffected [29]. Other studies suggested that indomethacin could decrease postoperative nitrogen excretion [1], and pyrexia [32,33], while the effects on leucocytosis and acute phase proteins are probably negligible [32,33]. No systematic study has been performed to compare the modifying effect of various nonsteroid anti-inflammatory agents on the surgical stress response. Neither is any clinical study available on pain relief produced by substance P antagonist administration or its eventual modification of the stress response.

The analgesia produced by hypothermia is well known in patients with burn injury, but this has not been utilized in surgical patients. Nevertheless, recent observations during hypothermic anaesthesia in experimental and clinical studies suggest that postoperative proteolysis may be attenuated [12]. Further studies, also addressing a possible modification of the inflammatory reaction, should be performed.

Glucocorticoids are potent inhibitors of all the metabolites of the arachidonic acid cascade as well as of several of the metabolically active macrophage-derived peptides. Although glucocorticoids may have potential side effects on wound healing and immunofunction, it is most interesting that a single, large preoperative dose of methylprednisolone led to improved pain relief and reduced need for extradural analgesics. In addition, the hyperthermic response was blocked and postoperative impairment in pulmonary function and fatigue decreased [Schulze and colleagues, in preparation]. Obviously, further studies are necessary, but it should be emphasized that glucocorticoids remain the only therapeutic agents with potential multi-inhibitory effects on the various components of the stress response.

Local anaesthetics may be applied directly to the nociceptors by a number of routes—i.v., intrapleural, i.p. and incisional—with varying degress of pain relief [15]. The effect of i.v. administration of local anaesthetics on postoperative pain is controversial, but probably does not significantly affect the postoperative stress

TABLE I. *Effect of extradural or intrathecal local anaesthetics on the endocrine-metabolic response to lower abdominal (gynaecological) surgery, prostatectomy and procedures on the lower extremities.* (*Data from* [*14*] *and* [*16*])

Type of response	Inhibition or improvement	No important effect	No data
Pituitary	ACTH	T_3 and T_4	Gastrointestinal peptides
	β-endorphin	Coagulation and fibrinolysis	Testosterone
	GH	Acute-phase proteins	Estradiol
	AVP	Water and sodium balance	
	TSH		
	LH and FSH		
	Prolactin		
Adrenal/Renal/ Nervous system	Cortisol		
	Aldosterone		
	Adrenaline		
	Renin		
	Noradrenaline		
Metabolic	Hyperglycemia and glucose tolerance		
	Lipolysis		
	Muscle amino acids		
	Nitrogen balance		
	Oxygen consumption		
	Urinary potassium excretion		

response [3,4,43]. Intrapleural administration of bupivacaine may provide reasonable pain relief after cholecystectomy, kidney surgery, *etc.* [5], but the modifying effect on the stress response and pulmonary function is negligible [35]. I.p. instillation of large doses of bupivacaine has probably no analgesic effect [37,42], and the effect on the stress response is probably insignificant [30,37,42]. Incisional application of local anaesthetics may provide some pain relief [15,40], and preliminary studies of the minor injury produced by inguinal herniotomy suggest some modification of the stress response [40]. However, one should not expect any important modification after major surgical injury.

Regional anaesthesia

The effects of regional anaesthesia (extradural or intrathecal) on the endocrine metabolic response have been reviewed in detail recently [14, 16] and will only be summarized here (table I). Most studies in which a pronounced inhibitory effect has been observed involved operations such as hysterectomy, vaginal surgery, inguinal herniotomy, minor orthopaedic procedures, prostatectomy and hip replacement. In contrast to these studies of operations on the *lower* part of the body, more than 20 studies of extradural analgesia and the stress response to procedures in the upper abdomen and thorax have failed to show a similarily pronounced inhibitory effect. However, a large variation has been found in the effect of regional anaesthesia on specific endocrine and metabolic changes after upper laparotomy. Unfortunately, interpretation is hindered by lack of control of the degree of sensory block, information on the amount of local anaesthetic administered, degree of pain relief *etc.* [14,16]. Despite these flaws in methodology, it seems valid to conclude that neural block, as produced by extradural analgesia, is less efficient in decreasing the surgical stress response to upper abdominal and thoracic procedures than in decreasing the response to lower body operations. Possible explanations for this are:

(1) Unblocked vagal afferents (but experimental and clinical studies suggest that these are unimportant [14]).

(2) Unblocked phrenic afferents. No information is available.

(3) Insufficient afferent and efferent sympathetic blockade. The addition of a coeliac plexus block has been shown to decrease the stress response further during extradural analgesia [14], and intraoperative splanchnic nerve block decreased several responses during gastrectomy [39]. However, the degree of sympathetic block during regional anaesthesia is under debate [8], and interpretation of the available studies therefore becomes difficult.

(4) Insufficient afferent somatic block. This is probably the main explanation for the lack of

important effects of extradural local anaesthetics on the stress response to upper abdominal surgery. Studies using evoked potentials have demonstrated that the afferent block is insufficient during thoracic extradural analgesia with conventional doses of bupivacaine [20]. This discrepancy in efficacy between a thoracic extradural and lumbar extradural block is easily understandable, since the amount of local anaesthetic administered during a thoracic extradural technique is less than 50% of that used during a lumbar technique.
(5) The role of unblocked pelvic parasympathetic afferents is unknown.
(6) Potentiating humoral release mechanisms and increased heat loss may also contribute to the decreased effect of regional anaesthesia during major (and long) operations.
The effect of continuous intrathecal block during major procedures has not been studied, but such a block may be expected to be more efficient in decreasing the surgical stress response.

The effect of a pure somatic block with bilateral intercostal nerve block has been addressed in one study. There was no effect on the plasma cortisol response and only a slight inhibitory effect on the glucose response [24]. The effect of continuous paravertebral block on the surgical stress response to upper laparotomy has not been studied, but no major effect would be expected. The administration of 0.5% bupivacaine 5 ml h^{-1} only provided a moderate degree of pain relief [2].

Thus studies published during the past 2 years have not provided much new information on the inhibitory effect of different regimens of central neural block on the surgical stress response, and further studies should focus on the effect of a more intense block by continuous intrathecal local anaesthetic administration or even combined extradural and intrathecal administration.

Spinal opioids

The effect of extradural or intrathecal opioid administration on the surgical stress response has been reviewed in detail [14,16]. There is general agreement that, despite reasonably good postoperative pain relief, these techniques have no major effect on the surgical stress response, although occasionally an inhibition of some stress parameters has been demonstrated. These studies have therefore emphasized that pain relief *per se* does not necessarily lead to a decrease in the surgical stress response.

Spinal α-adrenergic agonists

The intrathecal or extradural administration of α-adrenergic agonists has been shown experimentally to modulate spinal nociceptive processing [44] and some preliminary clinical studies have shown a small or moderate effect on postoperative pain, or a potentiating effect on local anaesthetic action [21,26]. In a study comparing extradural clonidine 150 μg with extradural morphine 4 mg after hysterectomy, an almost similar, moderate effect on postoperative pain was obtained, but only a slight modulatory effect on the surgical stress response [21]. No studies are available on the combined effect of extradural clonidine and morphine.

Systemic opioids

The moderate degree of pain relief produced after major procedures by conventional doses of intermittent or continuous opioids has only a negligible effect on the surgical stress response [14,16]. In a study using patient-controlled administration of fentanyl after cholecystectomy, no important effect could be demonstrated on plasma catecholamine or glucose response while postoperative cortisol concentrations were moderately diminished, despite very good pain relief [23]. Thus although there are few available data, optimal pain relief by systemic opioid administration cannot be expected to have an important modulatory effect on the surgical stress response. Very large doses of systemic opioids are necessary if a pronounced decrease in the stress response is required [14,17].

Combined analgesic regimens

Since total postoperative pain relief cannot be achieved by a single agent or method without major expenditure on equipment and surveillance systems, or without significant side effects, recent efforts have focused on improving pain relief by combinations of agents. Thus combining extradural local anaesthetics (0.5% bupivacaine 5–8 ml h^{-1}) with morphine 0.5 mg h^{-1} provides total pain relief even after upper abdominal surgery [9,36]. However, this is at the cost of either lower extremity paralysis [9] or potential respiratory side effects [36]. The use of lower concentrations of local anaesthetics and morphine leads to less good pain relief [2,6,18,19].

Despite total pain relief after upper abdominal surgery with the combined technique, no significant effect was observed on the surgical stress response or the impairment in pulmonary function [36]. Similarily, a combination of extradural bupivacaine with morphine and systemic indomethacin led to total pain relief after cholecystectomy [32], but no clinically significant effect on the impairment in pulmonary function, convalescence or the stress response. These studies, therefore, clearly indicate that total pain relief after major surgery does not necessarily lead to an important decrease in the surgical stress response. Again, this is probably the result of incomplete afferent neural block with several fast conducting neural pathways functioning, despite sufficient block of the slow conducting and pain mediating C-fibres [16,20].

Although a combination of analgesic regimens will have a major place in the future treatment of postoperative pain [15], measures to provide concomitant modification of humorally mediated responses and techniques to improve afferent neural block should be explored. In this context the role of the addition of high dose glucocorticoid therapy should be investigated further. The use of intense intraoperative block by a combination of continuous intrathecal and extradural block may be clinically advantageous (Kehlet and colleagues, unpublished observations), probably because of a decrease in the peripheral and central hypersensitivity to pain that occurs after injury [41].

CLINICAL IMPLICATIONS AND SUMMARY

The clinical implications of pain relief and the variable decrease this produces in the surgical stress response are largely unknown. This is because there are surprisingly few data and those that exist only demonstrate minimal beneficial clinical effects on postoperative morbidity parameters other than pain relief. Thus no controlled study has been performed to evaluate the clinical effect of pain relief by inhibition of endogenous algesic substances. This also applies to the systemic administration of opioids, even when sufficient pain relief is obtained by patient-controlled analgesia.

Postoperative pain relief by extradural opioid administration after conventional extradural block with local anaesthetics probably has no major effect on postoperative morbidity (or the stress response) after major abdominal procedures [10,11,28], although one study in high risk patients has suggested a major decrease in several complications [46]. In contrast, a vast amount of data exist from controlled studies comparing regional anaesthesia with local anaesthetics and general anaesthesia [34]. Cumulated data, mostly from procedures in the lower abdomen, orthopaedic or urological surgery, demonstrate a beneficial effect of regional anaesthesia on postoperative morbidity parameters such as blood loss, thromboembolic complications, pulmonary infection, gastrointestinal motility and postoperative hospital stay [34]. Interestingly, the most pronounced effect on morbidity occurred in procedures where regional anaesthesia with local anaesthetics also most effectively reduced the stress response. However, the important question whether this represents a causal relationship or an incidental event has not been finally answered.

To summarize, analgesia *per se* may not necessarily have an important effect on the surgical stress response, but is highly dependent on the technique used to provide postoperative pain relief. Furthermore, the effect of pain relief *per se* on postoperative morbidity is probably not a major one, unless the technique also concomitantly decreases the surgical stress response. Future studies should continue to decribe the role of the various release mechanisms of the surgical stress response and to evaluate modifying techniques, in the hope of further decreasing postoperative morbidity.

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Br. J. Anaesth. (1989), **63**, 196–206

ANALGESIA AND SEDATION IN INTENSIVE CARE

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Most patients admitted to an intensive care unit (ICU) require analgesia, sedation or both during at least part of their stay. However, the methods used to achieve these are often determined by tradition and convenience rather than by the needs of the patients, who are exposed to a number of noxious stimuli. These include relatively constant factors such as pain after trauma or surgery, distress and discomfort from the presence of a tracheal tube and mechanical ventilation, environmental noise, and anxiety from appreciation of the severity of the illness. In addition, intermittent stimuli occur during physiotherapy, tracheal suction and nursing procedures such as turning and changing of dressings.

ASSESSMENT OF NEED

The relative requirements for sedation and analgesia depend on the presenting condition, the severity of illness and the intensity of treatment. Clearly, some type of analgesia is required for patients who have suffered trauma or undergone surgery, and opioids may be useful to suppress the cough reflex and respiratory drive in those who require tracheal intubation and mechanical ventilation. In addition, sedative agents may be necessary to allay anxiety. Sedatives may also be appropriate alone in some categories of patient, for example those with primary respiratory failure or neuromuscular disease. In patients with cerebral pathology and intracranial hypertension, sedative drugs may form a part of therapy, but in most patients sedation and analgesia are provided primarily to ensure comfort, and side effects or interactions with other drugs may produce undesirable consequences.

Few studies have attempted to identify the need for sedation in ICU patients. In general, attitudes towards sedation are influenced by three factors.

Informed anecdote

Several nursing and medical personnel who have been patients in an ICU have described their experiences [18, 49, 57]. The most notable features of these recollections are pain, anxiety and disorientation. The use of neuromuscular blocking drugs caused particular concern. However, it is possible that the existing knowledge of nursing or medical staff may have influenced their fears and anxieties.

Subjective impressions

Follow-up of ICU patients has also demonstrated that many patients experience pain and discomfort as a result of inadequate sedation and analgesia [6, 34, 36]. Bion [6] interviewed 60 patients after their discharge from a general ICU and the results of his study are shown in table I. The commonest recollections were of physiotherapy and of the presence of a urinary catheter, although these were not found to be particularly distressing by the majority of patients. Anxiety was the most commonly reported unpleasant phenomenon, but 67 % of patients recalled thirst, and 60 % of these found it moderately or very

TABLE I. *Recall of distressing experiences by 60 ICU patients. (Adapted, with permission, from Bion* [6])

Experience	Percentage who recalled experience	Percentage who found experience unpleasant
Anxiety	55	78
Pain	40	67
Lack of rest	45	63
Thirst	67	60
Tracheal tube (50 patients)	38	57
Face mask	67	52
Nasogastric tube	57	47
Physiotherapy	75	33
Urinary catheter	75	17
Nausea	13	12
Paralysis (16 patients)	13	100

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unpleasant. Pain, lack of rest, the presence of a tracheal tube and application of a face mask were also found to be unpleasant by the majority of patients who recalled these stimuli. Only two patients remembered being paralysed, but both found it unpleasant.

Bion also related the accuracy of patients' recollections to time, the drugs received and the severity of illness. Patients tended to have a poor recollection of the early part of their admission. Midazolam reduced significantly the accuracy of recall, and recollection was impaired to some extent in patients with a high APACHE II score [39] at the time of admission.

Objective assessment

There is at present no satisfactory objective measure of sedation or analgesia in the ICU patient other than regular clinical assessment of the patient (see below). Changes in arterial pressure and heart rate are likely to be inaccurate indices of sedation because of the effects of the patient's illness on these parameters, although they may indicate the reflex response to acute intermittent stimuli. Plasma catecholamine concentrations have been used to assess the magnitude of response to noxious stimuli during anaesthesia [15]. Concentrations of both adrenaline and noradrenaline are substantially higher than normal in ICU patients who are deeply sedated as judged by clinical criteria, and increase significantly during chest physiotherapy [2], a stimulus which is known also to increase arterial pressure, heart rate and intracranial pressure [26].

FACTORS WHICH INFLUENCE DRUG REQUIREMENTS

The requirement for pharmacological sedation may be reduced by a number of factors.

The severity of the patient's illness may influence the dosage of analgesics necessary to achieve adequate sedation. In patients with a high APACHE II score, deeper levels of sedation are achieved at lower plasma morphine concentrations than in patients who have less physiological disturbance [8].

Frequent communication and reassurance can do much to allay anxiety, and are essential in every patient. The importance of communication by staff was highlighted by the report [49] of a former ICU nurse who, after discharge as a patient in an ICU, drew attention to the fear and anxiety associated with even the most minor procedure carried out by staff without prior explanation. Although the staff had tried hard to provide information about the time of day, the date and the month, she found that her memory span was short, and found herself frequently disorientated.

Lack of windows in an ICU deprives patients of the normal day–night cycle and of information on seasonal and weather changes; the incidence of delirium in ICU patients is more than doubled if they are managed in a windowless room [67].

Intermittent mandatory ventilation reduces the discomfort and distress associated with mechanical ventilation by permitting the patient to take spontaneous breaths on demand. Moderate hypocapnia reduces respiratory drive and improves toleration of mechanical ventilation. Nasotracheal intubation is tolerated better than orotracheal intubation by most patients. Insertion of i.v. or intra-arterial cannulae causes pain and distress which may be obviated by the use of infiltration with local anaesthesia.

IDEAL LEVEL OF SEDATION

In a survey of the sedative techniques used in ICUs during 1978–79 [43], Merriman reported that 68% of units regarded the ideal level of sedation as that at which the patient was completely detached from the environment and was woken only occasionally; an even higher percentage regarded this level as ideal for patients who were very ill. However, in a larger survey conducted in 1986, Bion and Ledingham [7] found that physicians in 69% of units believed that patients should be maintained "asleep, but easily rousable". Excessive sedation with most of the available drugs leads to prolonged recovery times. In addition, large doses of i.v. anaesthetic

TABLE II. *Scoring system for assessment of sedation in ICU patients* [52]

Level	Response
1	Anxious, and agitated or restless, or both
2	Co-operative, orientated and tranquil
3	Responds to commands only
4	Asleep, but brisk response to glabellar tap or loud auditory stimulus
5	Asleep, sluggish response to glabellar tap or loud auditory stimulus
6	No response

agents [64] or opioids [64] appear to reduce immunocompetence and may be associated with an increased risk of infection.

The Glasgow Coma Score [62] is unsuitable for ICU patients. It was designed to assess patients with neurological deficit. In ICUs, limbs may be immobilized by splints or pain and the verbal responses impossible to elicit because of the presence of a tracheal tube. Linear analogue scores completed by nurses are of unproven accuracy in controlling analgesic and sedative drugs; analgesia, anxiety and sedation must be assessed separately and, although the technique may be useful for investigative purposes, it is probably not appropriate for routine use.

Ramsay and colleagues [52] described a six-point sedation score which is of practical value in a general ICU (table II). In most patients, adjustment of doses of sedative drugs to maintain a level between points 2 and 3 on their scale is desirable. This ensures that the patient is comfortable, and minimizes the risks of prolonged sedation and respiratory depression when administration is discontinued. However, additional intermittent doses of sedative or analgesic drugs are more likely to be necessary during physiotherapy or nursing procedures if patients are maintained at this level of sedation.

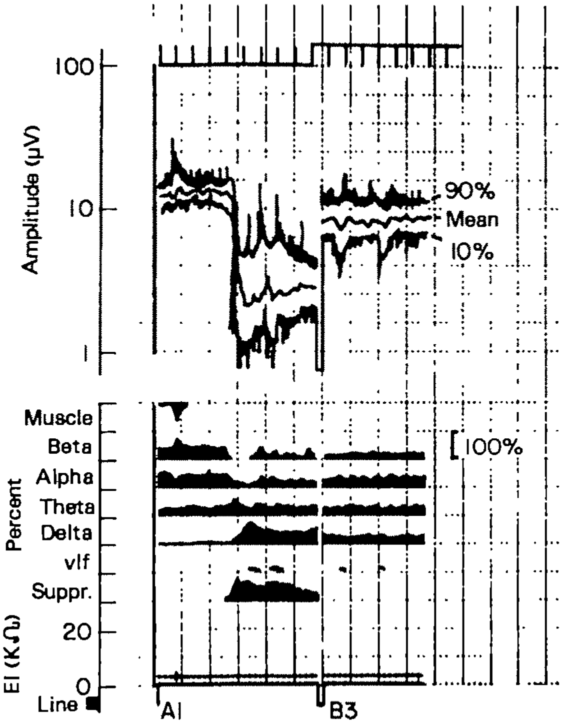

FIG. 1. A simulated trace from the cerebral function analysing monitor (CFAM). The top trace shows the mean (with 10th and 90th centiles) of the weighted amplitude distribution. In the lower half of the trace, muscle activity (Muscle), suppression (Suppr.) (percentage time that the weighted EEG is below a preset amplitude) and electrode impedance (EI) are plotted, together with the percentages of weighted EEG activity in the beta, alpha, theta and delta bands, and the percentage of very low frequency (vlf) activity. (Reproduced with permission from [42].)

Electrical or mechanical monitoring of conscious level is expensive and relatively insensitive. The cerebral function analysing monitor [42] displays a processed electroencephalogram (EEG) as the mean, 10th and 90th centiles of EEG amplitude distribution, together with the relative distribution of EEG frequency in the beta, alpha, theta and delta bands (fig. 1). Increased beta activity is associated with arousal, but the distribution of frequencies during sedation varies with the drug group used. Burst suppression may be detected by an increase in breadth of the amplitude distribution. The CFAM is influenced also by sepsis [35] and by pathological coma.

The frequency of spontaneous oesophageal contractility and the amplitude of secondary oesophageal contractions increase during stress, and tend to be decreased by analgesic, sedative and anaesthetic agents [22]. Measurement of lower oesophageal contractility has been used to monitor and control the sedation of ICU patients [23], but there is considerable interindividual variability in the response of the oesophagus to anaesthetic drugs [21] and the technique has not been proved to be a useful monitor in the ICU.

METHOD OF ADMINISTRATION

Most sedative and analgesic drugs are administered parenterally in the ICU. Sedation is achieved most satisfactorily by continuous i.v. infusion, a technique which avoids the peaks and troughs of analgesia and sedation associated with the use of intermittent i.m. or i.v. administration. The rate of infusion should be tailored to the patient's requirements, and usually requires adjustment from time to time. It is usually preferable to initiate sedation with a relatively rapid infusion, rather than by a bolus dose which may result in undesirable cardiovascular depression. In addition, it is often necessary to supplement the basal infusion with small increments of a rapidly acting agent (e.g. i.v. anaesthetic, fentanyl or alfentanil) or with an inhalation anaesthetic before painful procedures; this is of importance particularly in patients with intracranial hypertension, in whom painful stimulation may cause an acute and dangerous increase in intracranial pressure secondary to arterial hypertension, coughing and straining.

Other routes of administration may be appropriate in some patients. In general, the oral route is unsatisfactory because many drugs undergo extensive first-pass metabolism in the gut wall and liver, and because gastrointestinal motility is often decreased in the critically ill or postoperative patient. The buccal route is inappropriate in the patient with impaired consciousness. Rectal administration of non-steroidal anti-inflammatory drugs has been used successfully in the treatment of postoperative pain [53], and incorporation of opioids in hydrogel suppositories [27] is now being studied. The transdermal route of administration of opioids is also being investigated.

DRUGS USED FOR ANALGESIA AND SEDATION

Analgesics

Opioids are the most commonly administered drugs for sedation in ICUs. In a recent survey [7], 37% of units used an opioid drug alone for routine sedation, and a further 60% used an opioid in combination with a benzodiazepine. Opioids are appropriate for any patient in whom pain is anticipated, although the infusion rate must be titrated carefully in patients in whom artificial ventilation of the lungs is not anticipated. In the artificially ventilated patient, the antitussive action of the opioids may help toleration of a tracheal tube. The dose of opioid required is dependent in part upon the severity of the patient's illness [8]. Opioid dependence is extremely uncommon in ICU patients unless administration is continued for several days in a patient who is not in pain [43].

Morphine

Morphine is an appropriate drug in many situations in the ICU, although only 20% of units in the United Kingdom use it at present [7]. Its slow distribution half-life and relative lipid insolubility are disadvantages if a rapid onset of action is required, but in the patient in whom sedation will be required for many hours or several days, analgesia can be achieved by a loading dose followed by a continuous infusion. Adjustment of the dose results in a relatively slow change in level of analgesia. A loading dose of 10–15 mg followed by an infusion of 2–3 mg h^{-1} is an acceptable initial regimen in the adult. However, as with all opioid drugs, there is enormous interindividual variation in both pharmacokinetics and pharmacodynamics, and the dose must be adjusted for each patient.

Distribution volumes and protein binding may be abnormal in the ICU patient, resulting in an exaggerated or diminished response. However, morphine is less protein-bound than other opioids. The clinical effect of alterations in hepatic function on its metabolism is small, although clinical factors which reduce hepatic blood flow, such as shock, would be expected to reduce the elimination of the drug. The main disadvantage of morphine in the ICU patient relates to the elimination of its metabolites, which are normally excreted in the urine. One of the main metabolites, morphine-6-glucuronide (M6G), is several times more active than morphine itself in animals [56]. Blood concentrations of M6G may reach high values after prolonged infusions, particularly in patients with impaired renal function [48]. Thus the infusion rate may have to be decreased after some hours, and there may be a much longer delay between cessation of the infusion and diminution of clinical effect than the elimination half-life (table III) might suggest. If very large doses have been used, respiratory depression and excessive sedation may last for more than 24 h.

In the presence of hypercapnia, the volume of distribution of morphine is decreased, and serum and brain concentrations are increased after a bolus dose of morphine [25]. In addition, the half-life of morphine in the brain is prolonged by more

TABLE III. *Approximate distribution and elimination half-lives of opioid agents in normal patients. *The clinical effects of buprenorphine are related poorly to serum concentration because of receptor binding*

Agent	Distribution half-life (min)	Elimination half-life (h)
Morphine	25	1.5–4
glucuronides		3–6
Fentanyl	3	2–5
Sufentanil	1	2–3
Alfentanil	3	1.5–3.5
Phenoperidine	3	1.5–4
Pethidine	7	3–6.5
Nalbuphine	2	3.5–4
Buprenorphine*	3	2–4.5

than 50 %. These differences are thought to result from acidaemia rather than hypercapnia *per se*, and a similar effect may occur in the presence of metabolic acidosis.

Morphine causes a naloxone-reversible depression of the primary immune response in mice [32]. Large doses of morphine administered for several days decrease reticuloendothelial system activity and phagocytosis in guineapigs [40], mice and rabbits [63] and render animals more susceptible to infection. This effect is dose-related, and is not reversed by the administration of naloxone. In man, the incidences of bacterial and viral infections are high in heroin addicts [11]; these infections have been attributed in the past solely to the use of contaminated drug, syringes and needles, but may be related to the decreased macrophage numbers and activity demonstrated in small animals. It is not clear at present whether this effect, which has obvious implications in the ICU patient, is common to all opioid drugs.

Papaveretum

The analgesic effects of this drug are predominantly attributable to the morphine which it contains, but the other alkaloids appear to provide more of a sedative effect than morphine alone. This may be an advantage in many patients, but can result in prolonged narcosis if large doses are given, particularly to elderly patients or those with hepatic or renal impairment. Papaveretum has retained popularity as a sedative in British ICUs; it was used frequently by 32 % of units in the late 1970s [43], and was the preferred opioid in 33 % of units in 1987 [7].

Fentanyl

This drug is often thought to be superior to morphine or papaveretum because of its short duration after a single bolus dose. However, this effect is the result of its high lipid solubility, which permits rapid equilibration between blood and central nervous system. As the drug is also distributed into other tissues, blood and CNS concentrations decay within a few minutes, and its analgesic and respiratory depressant actions wane. After repeated administration of fentanyl or after prolonged infusion, blood and CNS concentrations decrease only as the drug is metabolized, because distribution into other tissues has already occurred. The elimination half-life of fentanyl is longer than that of morphine (table III) after a single bolus dose; in the elderly, the elimination half-life is extended to 9 h, and may be as long as 16 h after a prolonged infusion [54]. Consequently, fentanyl is *not* a short-acting drug when used for analgesia in the ICU, and offers little advantage over morphine.

Alfentanil

Alfentanil has a small distribution volume and short terminal half-life in most patients. Consequently, it should be a useful drug for administration by infusion, as changes in infusion rate should produce a rapid alteration in clinical effect. However, it is an expensive agent. Although its use has been reported as satisfactory in a small number of ICU patients [12], it had no advantages over pethidine in another study [68]. In addition, its elimination is delayed and its duration of action prolonged in some patients [68]. When a prolonged period of analgesia is anticipated, it may be appropriate to use alfentanil to establish analgesia rapidly before changing to use of another opioid; its use might also be considered towards the end of the treatment period to decrease the risks of prolonged respiratory depression when the infusion is discontinued.

Pethidine

Pethidine is a useful alternative to morphine, especially in patients prone to bronchospasm. It is rather more lipid soluble than morphine, and its actions are therefore of more rapid onset. At low infusion rates, it is a useful analgesic in the spontaneously breathing patient, and it possesses relatively little sedative effect. However, it depresses myocardial function in high doses, and its major metabolite, norpethidine, has convulsant properties and may accumulate in patients with impaired renal function [37]. Blood concentrations of pethidine are increased in the elderly, and its elimination is delayed in patients with hepatic dysfunction.

Phenoperidine

This opioid drug, which is related to pethidine, was the most commonly used in the late 1970s [43], and is still the preferred drug in 27 % of British units [7]. However, there is no objective evidence that it has any advantage over other drugs. It may increase intracranial pressure [31] and its cardiovascular effects are rather more significant than those of other opioids. Phenoperidine causes peripheral vasodilatation, and arterial pressure decreases by up to 20 % in non-

ICU patients [51]. Several cases of profound cardiovascular depression have been reported in ICU patients after administration of phenoperidine [19, 28].

Agonist–antagonist opioids

Buprenorphine has a slow onset and prolonged duration of action, effects related to receptor binding rather than blood concentration. *Nalbuphine* has a relatively rapid onset, and a half-life of 3–4 h [1]. The main advantage claimed for these drugs is their "ceiling" effect in respect of respiratory depression. However, respiratory depression can occur with either agent; after buprenorphine, it may occur some time after administration, and is resistant to antagonism by naloxone [33]. In high doses, buprenorphine may antagonize its own analgesia. There may be a "ceiling" to the analgesic as well as the respiratory effects of these drugs.

Side Effects of Opioids

Respiratory

All pure agonist opioids decrease the rate and volume of ventilation, and decrease the sensitivity of the respiratory centre to carbon dioxide. It is likely that equianalgesic doses of any pure agonist result in equivalent degrees of respiratory depression. This side effect is often advantageous during controlled ventilation. However, infusions of opioids must be controlled very carefully in the spontaneously breathing patient if significant respiratory depression is to be avoided. In the ventilated patient, residual effects of opioids on the respiratory centre may delay weaning from the ventilator. The delay is to some extent unpredictable, even with the shorter-acting agents. The rate of elimination of opioids may vary by a factor of five even in normal individuals, and impaired metabolism and excretion, together with accumulation of metabolites, may result in a very prolonged duration of action in some patients.

Cardiovascular

All opioids may decrease arterial pressure by causing arterial and venous dilatation. This effect is seen particularly in the hypovolaemic patient. In clinical doses, myocardial depression is minimal [38]. In addition, an initial decrease in arterial pressure may result from the alleviation of pain and anxiety. The use of phenoperidine is associated with a greater decrease in arterial pressure than most other opioids. Fentanyl has less depressant effect on the cardiovascular system than morphine in patients with cardiac disease [41]. Pethidine has a vagolytic action which results in an increase in heart rate. The cardiovascular effects can be minimized by ensuring that the circulating volume is adequate, and by providing the initial loading dose as an infusion over 10–15 min rather than as a single bolus dose.

Gastrointestinal

All of the opioids delay gastric emptying and decrease intestinal motility. This may impair the ability to absorb enteral feeds, and may increase the risks of regurgitation and aspiration of gastric contents. Spasm of the sphincter of Oddi and an increase in common bile duct pressure may occur with all opioids, but the clinical significance of this in the ICU patient is not clear; this effect is antagonized by atropine, but not by naloxone.

Tolerance and addiction

Some degree of tolerance to opioids may occur after 3–4 days, and the infusion dose may have to be increased. Tolerance to both the analgesic and respiratory depressant effects occur. Addiction, reflected by withdrawal symptoms when the drug is discontinued, is excessively uncommon in patients who receive opioids for the treatment of pain, and fear of addiction should not limit dosage adjustments if tolerance develops.

Non-Opioid Analgesics

The combination of opioid and non-opioid analgesics may decrease the dose, and thus the potential for side-effects, of opioid drugs required to produce adequate analgesia. *Indomethacin* suppositories decrease the need for morphine after surgery [52] and have been used successfully to supplement opioids in patients with blunt chest trauma. However, haemorrhagic complications may occur. *Lysine acetyl salicylic acid* can be administered parenterally, and provides good postoperative analgesia [10].

Sedatives

Sedative drugs may be used alone, or in combination with opioids, to achieve sleep and anxiolysis in the ICU patient. As long as sufficient analgesia is achieved, not all patients require sedative drugs, particularly after the first 24–48 h of admission. It is inappropriate to use high doses of opioids alone to achieve deep sedation, as the doses required may result in prolonged respiratory depression. Similarly, it is inappropriate to use sedative agents alone for patients who are in pain, as anaesthetic doses are required. If patients have no source of pain, then sedatives may be administered alone. In most patients, however, a balanced combination of analgesic and sedative drugs titrated to individual needs results in relief of pain and anxiety, but permits continued communication with staff.

Benzodiazepines

These agents induce sleep, anxiolysis and a decrease in muscle tone. Although total sleep time is increased, there is a reduction in REM sleep [4]. *Diazepam* has an elimination half-life of 36 h and an active metabolite, N-desmethyl diazepam, with an elimination half-life of up to 96 h [29]. Infusion of diazepam is therefore inappropriate, and it is best administered as a loading dose with maintenance doses every 12–24 h. Recovery of consciousness may take several days if large doses are administered. Diazepam causes severe thrombophlebitis if administered into a peripheral vein, although the incidence of this complication is very low when the lipid emulsion formulation (Diazemuls) is used.

Flunitrazepam and *lorazepam* have long half-lives (20 and 15 h, respectively) and lorazepam also has a slow onset of action.

Midazolam has a rapid onset of action and a shorter duration of action in normal individuals than diazepam, flunitrazepam or lorazepam. It is water-soluble and can be administered safely into peripheral veins. Its elimination half-life in normal individuals is 2–4 h after a single dose, although this may be prolonged significantly in critically ill patients [55]. Although one of the metabolites, alpha-hydroxy midazolam, is active, it has an elimination half-life of only 1 h. Because of first-pass metabolism, alpha-hydroxy midazolam concentrations are higher after oral than after i.v. administration, and the metabolite contributes to the sedative actions of the drug [14]; however, the prolonged action of midazolam in ICU patients is likely to be the result of impaired hepatic metabolism rather than accumulation of metabolities. It may be difficult to detect clinical differences between midazolam and diazepam when administered in repeated doses [17]. In 1987, 45% of British ICUs used diazepam (as Diazemuls), and 39% midazolam [7]; lorazepam, which was popular in the late 1970s [43], is now used infrequently.

Although the benzodiazepines produce profound amnesia, they often fail to achieve satisfactory sedation. Amnesia *per se* may not prevent subsequent psychological sequelae after traumatic experiences; indeed, memory may be improved by benzodiazepines in anxious individuals [16]. All of the benzodiazepines tend to produce cardiovascular and respiratory depression. In addition, doses required to produce satisfactory sedation in the ICU patient often obliterate verbal contact with the patient and also result in significant delays in recovery if administration is prolonged.

The imidazobenzodiazepine, flumazenil, has been marketed recently as a benzodiazepine antagonist. The manufacturers recommend its use to antagonize the sedative effects of benzodiazepines to allow return to spontaneous ventilation and consciousness in patients in intensive care. However, its properties in the critically ill patient have not yet been investigated adequately. Its half-life is short and sedation and respiratory depression may recur unless an infusion of flumazenil is used for a prolonged period [9]; specific information about its half-life in the critically ill patient is limited. Rapid antagonism of sedation may result in hypertension and tachycardia. The effects of prolonged infusion of midazolam may not be antagonized at all [19]. Although flumazenil may offer a solution to the problems of prolonged recovery after benzodiazepine administration in the ICU patient, the use of antagonists to expedite recovery after therapeutic doses of drugs has inherent disadvantages, and it is the author's opinion that, in general, agonist drugs with rapid elimination and recovery are to be preferred.

I.v. anaesthetics

Barbiturates. Thiopentone and pentobarbitone are indicated occasionally in patients with severe head injury, as they help to control intracranial hypertension. However, after prolonged administration, slow elimination results in protracted coma. In moderate doses (approximately 100 mg h^{-1}) for up to 14 days, recovery of consciousness takes up to 48 h. In doses large enough to produce an isoelectric EEG, recovery may take up to 4 days [59]. Deep coma induced with thiopentone for treatment of patients with head injury has been associated with increased incidences of sepsis and adult respiratory distress syndrome [64], possibly as a result of reduced immunological competence. Barbiturates in high doses may result in significant cardiovascular depression.

Etomidate. This agent was used widely for sedation in the ICU after its introduction, although no properly conducted clinical trials had been undertaken to confirm its safety during prolonged infusion. Careful audit in one unit resulted in the detection of increased mortality associated with infective complications in a group of trauma patients who had received etomidate [65]. Further investigations revealed that etomidate induces adrenocortical suppression, even after a single dose [45]. It is, therefore, entirely unsuitable as a sedative agent in the critically ill patient.

Propofol. This new agent is insoluble in water, and is formulated in a lipid emulsion. It has a short elimination half-life and recovery of consciousness from anaesthesia after a single bolus or short infusion is free of the "hangover" associated with the use of most other i.v. anaesthetic drugs.

Only limited information is available regarding the safety of propofol for sedation in the ICU. It has been used successfully for 2.5–18 h after cardiac surgery [30]. The use of propofol was associated with more easily controlled sedation than midazolam, and a shorter requirement for mechanical ventilation; the median time from discontinuation of the infusion to the return of spontaneous ventilation was 9.5 min after propofol and 202 min after midazolam. A pilot study [47] in which propofol was used for 8 h in 10 ICU patients confirmed that the drug was useful and readily controllable as a sedative agent, but noted that critically ill patients might be particularly sensitive to the cardiovascular depressant properties of the drug.

In a recent multicentre study [Aitkenhead AR and colleagues, in preparation] 101 patients were allocated randomly to receive either propofol or midazolam, in combination with a continuous infusion of morphine 2 mg h^{-1}, for up to 24 h. The level of sedation was adjusted easily during infusion of propofol 1–3 mg h^{-1}, and communication was maintained with the patients (Ramsay scale points 2 or 3 (table II)). Consequently, there was no difference between midazolam and propofol in respect of recovery of consciousness, but propofol was superior in a subgroup of patients observed for recovery to the point at which weaning from artificial ventilation could be considered. Decreases in arterial pressure did occur with propofol, but were not significantly different from those caused by midazolam and responded to i.v. fluid infusion; it was never necessary to discontinue the administration of propofol because of side effects. Heart rate was slower with propofol. There were no biochemical abnormalities attributable to either drug. Although cortisol concentrations decreased during the infusion of both drugs, there was no inhibition of the Synacthen test. The lipid solution was not associated with any adverse effects.

In a small number of ICU patients who received propofol because of severe agitation, there appeared to be minimal accumulation of the drug over a 4-day period, and recovery times, which were assessed every 24 h, remained rapid ($<$ 30 min) [5]. However, it must be stressed that experience with this agent is limited. The drug is cleared more slowly in the presence of renal insufficiency [46] and the safety of infusion for longer than 24 h has not been established.

Chlormethiazole. This drug is used occasionally to sedate ICU patients. It produces little cardiovascular depression, and may increase heart rate and arterial pressure. However, it is formulated for i.v. use in a dilute solution, and large volumes are required to provide sedative doses. It is metabolized slowly in patients with hepatic dysfunction, and this may result in prolonged recovery of consciousness. Nevertheless, some units find it to be satisfactory in selected patients.

Ketamine. This drug has analgesic properties at subanaesthetic doses (0.5 mg kg^{-1}). However, its use as a sedative has been disappointing except in patients with severe bronchospasm, in whom it has been used successfully [60].

Inhalation anaesthetic agents

Virtually all of the inhalation anaesthetic agents have been used to produce sedation in the ICU. Not all possess analgesic activity at subanaesthetic concentrations. *Nitrous oxide* is useful in providing intermittent analgesia, for example during physiotherapy or other painful procedures. Concentrations up to 70% have been used, but may be limited by the requirement of the patient for a high inspired oxygen concentration. Prolonged use of nitrous oxide is associated with megaloblastic bone marrow changes [3]. Enflurane and isoflurane have also been used, but there have been no adequate investigations of the use of these agents for prolonged periods. Adequate scavenging facilities must be provided if inhalation agents are used.

Neuromuscular Blocking Drugs

A study published as recently as 1980 [44] showed that pancuronium was administered to "calm" 48 of 50 ventilated patients, and that it was by far the most commonly used drug for encouraging patients to tolerate artificial ventilation, in some cases without any sedation or analgesia. Thirty-one of 34 units surveyed in 1978–79 claimed to use pancuronium frequently, and a number of units used curare [43]. A subsequent editorial [20] drew attention to the dangers of paralysis in the conscious patient. Although nurses often prefer patients to lie still, and equate immobility with sedation, there are several important sequelae. Most distressing to the patient is awareness of pain, distress and paralysis [49]. In addition, the risk of hypoxaemia resulting from accidental disconnection from the ventilator is increased, pulmonary emboli are more frequent [61], the cough reflex is suppressed totally and peripheral nerve injury from incorrect positioning may occur [66].

Fortunately, the warnings have been heeded, and it is now uncommon for neuromuscular blocking drugs to be used in the ICU; only 16 % of units surveyed in 1986 used them, 71 % of these only rarely [7]. However, they are still indicated in some circumstances. In patients with severe hypoxaemia, oxygenation may be improved by using a neuromuscular blocker if chest wall compliance is increased, particularly if the patient is restless. In patients with intracranial hypertension, improved control of intracranial pressure may be achieved by neuromuscular blocking agents, probably because of an increase in venous capacitance secondary to a decrease in skeletal muscle tone. Muscle relaxants may be required also in patients with tetanus. Irrespective of the indication, it is *essential* to ensure that the patient is adequately sedated before any neuromuscular blocking drug is given.

Pancuronium achieved popularity in the ICU because of its tendency to increase arterial pressure. However, it also induces a tachycardia, and this may be a disadvantage in patients who may already have an increased heart rate as a result of disease. Vecuronium and atracurium have little effect on the cardiovascular system. However, vecuronium may accumulate in the critically ill patient [58], leading to prolonged paralysis. Atracurium is probably preferable if a neuromuscular blocking drug is indicated. A recent case report suggests that cumulation of the major metabolite laudanosine is minimal even after infusion of atracurium for 71 days [50], although concern has been expressed that laudanosine might accumulate in patients with renal insufficiency [24].

Regional Analgesia

Some patients in ICU may benefit from regional anaesthetic or analgesic techniques, although the presence of sepsis or coagulation defects are contraindications to the major regional techniques. Extradural administration of local anaesthetic drugs may result in unacceptable hypotension in the presence of hypovolaemia. In selected patients the administration of local anaesthetic drugs by continuous slow infusion provides analgesia with little cardiovascular depression, and may be of value in the patient with poor respiratory reserve after abdominal or thoracic surgery, or after blunt chest trauma. Extradural opioids may result in good analgesia without cardiovascular depression [13]; lipid soluble drugs such as fentanyl or diamorphine are more effective, and are associated with a lower incidence of respiratory depression than insoluble agents, for example morphine.

When appropriate, other local anaesthetic techniques such as brachial plexus or intercostal block may be used; the use of an indwelling catheter allows prolonged block to be achieved.

CONCLUSION

Sedation in the ICU must be tailored to the needs of each patient. The appropriate use of analgesic drugs or techniques may be used together with methods of reducing psychological stress to minimize the administration of sedative agents, thereby retaining verbal contact with the patient. The risks of delayed recovery of orientation and respiratory drive are decreased by avoiding excessively deep levels of sedation, and by using drugs which are metabolized and eliminated rapidly.

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Br. J. Anaesth. (1989), **63**, 207–212

RECENT ADVANCES IN THE TREATMENT OF CHRONIC PAIN

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The treatment of chronic pain is one of the most complex aspects of medical care and encompasses both the complete spectrum of conventional medicine (including both pure and applied sciences) and much of complementary medicine. This complexity means that advances of a significant nature may take place not only within the confines of the therapeutic milieu, but also in parallel disciplines such as administration, data collection, socio–economic management and even the philosophical and conceptual aspects of chronic pain relief. Indeed, it may be argued that the most important and far reaching advances in the treatment of chronic pain within the past two decades have been outside the direct therapeutic field. They have included the recognition that the psychological component of pain producing illness is of equal importance to the organic pathology so that the two need to be assessed and treated together, and an increasing acceptance of the need to provide a nationally integrated service to treat patients suffering from chronic pain. A burgeoning number of Health Districts are providing multidisciplinary pain relief services which are being integrated at local and national levels. Even in this latter aspect, change has taken place. The current understanding of "multidisciplinary" is that the input into patient care comes from several disciplines, both clinical and scientific, but co-ordinated by the consultant in charge of the pain relief service. This contrasts with the previously held concept that "multidisciplinary" meant that the patient was questioned and examined by representatives of all interested disciplines at the same attendance; this proved wasteful of both time and facilities. Nevertheless, clinical treatment has made great strides and may be considered in three main categories: psychological, pharmacological and physical.

PSYCHOLOGICAL THERAPY

It is now widely accepted that, in an illness, psychological factors will act together with organic ones to generate, maintain or worsen pain. In addition to this, illness behaviour patterns distinct from the complaint of pain, may be generated or modified, so further confusing the picture and rendering diagnosis, assessment of factor importance and treatment more difficult. Appreciation of the patient's psychological state, its assessment in parallel with the physical parameters, and their juxtaposition in a therapeutic schedule have comprised a major advance in recent years. From this has developed the following therapeutic triad:

(i) A single treatment modality is rarely indicated or successful.

(ii) The psychological approach to therapy must never be divorced from the physical one.

(iii) A treatment schedule containing both psychological and physical modalities should be constructed for each individual patient according to the particular needs of each.

Because 25% of patients with chronic pain exhibit overt symptoms and signs of depressive psychoneurosis, and a further 25% have a mental disorder which may be the primary complaint or secondary to the physical problem, the importance of delineating these patients from the "Normal" is emphasized by the need to treat the psychological illness in a specific way.

One way in which the cohort of depressed patients can be selected from the total group is by an assessment of their coping strategies [17]. In the whole group of patients, the primary attempt to control pain may be instituted using both physical and psychological techniques once the initial diagnosis has been made and any overt psychiatric illness treated. Psychological therapy is divided into three major types: psychotherapy, operant conditioning and behavioural therapy. Currently, in the United Kingdom the emphasis

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has moved towards individual and group behavioural programmes. The latter, whilst being conducted initially by the professional carers, may well become self perpetuating as the patients become successive group leaders [24, 48, 52, 61]. It is highly likely that the development of this area of therapy will continue apace, reinforcing the appreciation of the importance of psychological therapies in conjunction with the older established physical and pharmacological varieties. This conceptual change has been one of the more important advances made by those in Pain Relief Services in this country.

PHARMACOLOGICAL THERAPY

Primary Analgesics

Mu agonists

The introduction of sustained release formulations of some of the more commonly used mu agonist opioids has radically altered and improved the treatment of patients with pain from malignant disease and its consequences [4, 23]. The availability of morphine sulphate in a controlled release formulation (MST Continus, Napp) has been a significant step forward and, as the pharmacokinetics of the agent have become more widely appreciated, it has been used in an optimal manner. Realization that a strict twice-daily dose regimen is not always the best to produce adequate analgesia and minimal side effects has increased effectiveness, and the introduction of 60-, 100- and 200-mg tablets has improved patient compliance.

There has been a growing acceptance that, contrary to popular belief, the prescription of opioids does not inevitably lead to tolerance and dependence [26, 45]. Consequently, patients with pain of non-cancerous origin whose quality of life has been significantly reduced by their illness and for whom no other therapy has been successful are being treated by long term opioid therapy. This is proving that the quality of life can be improved, allowing many to return to work whilst revealing no acute or long term problems from tolerance or dependence [13]. The indications for opioid use in non-cancerous pain include severe pain with a significant reduction in quality of life, a proven diagnosis, no psychological contraindications and pain that is opioid sensitive. All other therapy should have been tried and failed and treatment should not be instituted without the co-operation of the General Practitioner. In spite of much available evidence indicating the value and safety of this treatment, the caring professions are finding the conceptual change hard to make and greater education is needed.

Metabolism. For many years there has been discussion and disagreement about the way in which the human body deals with exogenous opioids. Information on the metabolic pathways of opioids and the likelihood of metabolites possessing analgesic activity has now been correlated [38]. This knowledge, particularly that concerning morphine, has answered a number of contentious questions, thereby allowing these agents to be used in a more logical and pharmacokinetically sound manner. These and other aspects of the use of opioids in chronic pain are considered in more detail elsewhere in this issue [36].

Kappa and delta agonists

The existence of kappa and delta opioid receptors has been known for some time [15, 57, 63]. Although their characteristics have been demonstrated, the clinical introduction of drugs with agonist and antagonist actions at these receptors has been slow [43, 60]. Several partial kappa agonists have been in clinical use for some years, but the availability of pure agonists has been delayed by unacceptable side effects [44]. It would appear likely, however, that a new generation of drugs acting at the kappa and delta receptors may be investigated in limited clinical trials within a short time [12].

Opioid sensitivity

For a long time pain has been thought to be homogeneous in its response to analgesics, but there has been a realization that this is not so and that there is a wide spectrum of response to drugs, in terms of both agent and dose. Consequently, at a relatively simple level, pain may be described as being opioid sensitive or insensitive. This has led to a more rational approach to the use of drugs in both cancer and non-cancer pain. The majority of drugs that are used to treat the opioid insensitive pain fall into the category of secondary analgesics (see below).

Opioid antagonists

The opioid antagonist drugs such as naloxone, naltrexone and nalmefene have been used for a decade only to treat the adverse effects of opioid

TABLE I. *Psychoactive drugs used in the treatment of chronic pain*

Pharmacological action	Drug	Antidepressant effects
Monoamine oxidase-B selective inhibition	Deprenyl Selegiline	Fair
Selective 5-hydroxytryptamine reuptake inhibition	Trazodone Fluoxetine Fluvoxamine	Good
Selective noradrenaline reuptake inhibition	Maprotiline Nomifensine Viloxazine	Fair
Alpha receptor antagonists	Mianserin Idoxazan	Good
Central beta-receptor antagonists	Clenbuterol	Fair

agents, namely overdose and drug dependence. More recently, however, a place for naloxone in the treatment of shock syndrome and acute cerebrovascular accident has been established [19], and the value of opioid antagonists in the therapy of chronic pain of central origin, particularly that following stroke, has been demonstrated [7, 8]. After initial work with high dose i.v. naloxone, the availability in oral formulation of naltrexone and, subsequently, nalmefene, has made long term maintenance treatment for responding patients a much more realistic procedure.

Drug delivery systems

After the revelation that opioids would produce analgesia when administered intrathecally or extradurally, there was considerable interest in their administration by these routes, and by other methods and portals of entry into the body [16]. The proliferation of apparatus with which to deliver drugs to the presumed site of action has been great, but since the early enthusiasm there has been a more searching re-evaluation of such techniques so that their use is becoming more logical; safe and cost effective [11, 58]. The pioneering spirit is now concentrating on other routes of administration which may well bring safe, cost effective analgesia to sufferers of both acute and chronic pain in the near future [42, 59].

Non-steroidal anti-inflammatory agents (NSAID)

The many drugs in this group that are in clinical use at present would appear to have a well described and accepted mode of action. However, there seem to be major discrepancies between the degree of arachidonic acid cyclo-oxygenase inhibition exhibited by each drug and its observed anti-inflammatory and analgesic effects. Until an answer is found to this conundrum, the use of these agents in the conditions in which they are most valuable must remain empirical and based on clinical experience and judgement [33, 56].

Two more recently introduced NSAID, etodolac and sulindac, show no marked effects upon the renal prostaglandin synthetic enzyme systems. This, together with a lower incidence of gastrointestinal side effects, has suggested an avenue for the future development of drugs having the efficacy, but not the adverse effects of the NSAID in contemporary use [27, 30, 46].

Secondary Analgesics

Psychopharmacological agents

The introduction of newer psychoactive drugs has helped to elucidate which pharmacological effects are necessary for such an agent to be clinically valuable in the treatment of chronic pain (table I). One of the most recently introduced tricyclic antidepressant agents, fluvoxamine, has a selective blocking action on the re-uptake of 5-hydroxytryptamine (5HT) from the intersynaptic cleft [5]. This property is shared by other antidepressants such as trazodone and fluoxetine, but clinical use has shown that these agents are of much less value in the production of analgesia than their predecessors which exert an effect on a wider spectrum of catecholamine neurotransmitters (table II) [49].

The continued evaluation of the anticonvulsant drugs has confirmed their value in the treatment of neuropathic pain [53]. Whilst carbamazepine is probably regarded as the first choice of agent in

TABLE II. *Catecholamine neurotransmitters affected by the actions of various groups of drugs. MAOI = Monoamine oxidase inhibitor; 5HT = 5-hydroxytryptamine; NA = noradrenaline; DA = dopamine; ACh = acetylcholine; H = histamine; GABA = gamma-amino butyric acid*

Drug group	Neurotransmitter affected
MAOI	5HT, NA, DA
Tricyclic antidepressant	5HT, NA, DA, ACh, H
Phenothiazine derivative	DA, GABA, H
Benzodiazepine	GABA, NA
Butyrophenone	DA, NA
Anticonvulsant	GABA, DA

those patients whose pain is the result of nerve damage, entrapment or changed function caused by endocrine disorders, the use of sodium valproate, clonazepam and clobazam is seen to be of increasing value. These agents are used alone or, with better effect, in combination with a tricyclic antidepressant or phenothiazine derivative.

Cardiovascular drugs

Certain primary cardiovascular drugs have been used in the treatment of chronic pain for some time: beta-adrenergic blocking agents in the treatment of resistant migraine and guanethidine or bretylium in the isolated limb for sympathetic dystrophy are good examples. More recently, the 5HT2 antagonist, ketanserin, has been shown to be of some value in the treatment of algodystrophy and certain collagenoses such as Raynaud's Disease [25, 32]. The activity of ketanserin is essentially peripheral and the availability of centrally acting cogenors such as ritanserin will not only be of value clinically, but will also shed some light on the part 5HT plays in nociception, and its possible sites of activity.

Lignocaine has been used for some time as a diagnostic agent for assessing the value of membrane stabilizing drugs in neuropathic and dystrophic pain, after which those patients benefitting from lignocaine 100 mg i.v. are treated with oral anticonvulsant drugs for the longer term [53]. The introduction of two derivatives of lignocaine, tocainide and flecainide, gave further clinical aid in this difficult area. The results have been encouraging and a mode of action has been postulated, namely that in hyperexcitable nerve membranes, calcium channels are blocked, resulting in return to normal function [34, 35].

The value of specific calcium channel blocking agents has also been observed and both nifedipine and diltiazem have found a place in the treatment of peripheral ischaemic pain and of some of the more obscure peripheral neuralgic conditions. Although diltiazem is less potent than nifedipine, its side effect profile makes it more useful clinically [10].

Clonidine, when administered extradurally has been shown to produce worthwhile analgesia in both cancer and non-cancer pain [21]. Evidence has also shown that extradural or intrathecal clonidine may enhance the analgesic effect of opioids when they are administered together [14].

Miscellaneous drugs

Baclofen, one of the neuromuscular blocking drugs, may, when given intrathecally, reduce the pain and spasm experienced by patients with traumatic transection of the spinal cord (Glynn CJ, personal communication). Whether other such agents, or GABA agonists, will produce the same result has yet to be explored.

Disseminated bone metastases from primary malignant disease of breast or prostate not infrequently produce widespread pain which may not respond to opioids or physical therapy such as nerve block. Both calcitonin and mithramycin have been shown to have analgesic activity in these conditions [1, 31, 50, 51]. L-Dopa can be used also to treat the pain of prostatic cancer metastases and certain peripheral neuralgias [28, 37], in particular post-herpetic neuralgia.

PHYSICAL THERAPY

Traditionally, pain relief by physical therapy has been achieved through the application of cold, heat, chemicals or the surgeon's knife to peripheral or central nerves. The more recent advances in physical analgesia have been not in nerve destruction, but in neuronal stimulation.

Stimulation techniques

Transcutaneous electrical neural stimulation (TENS) is now widely used for the treatment of chronic pain. In dorsal column stimulation (DCS), electrodes are introduced percutaneously to the posterior extradural space. When current is passed, stimulation of the dorsal columns of the spinal cord produces a descending inhibitory stimulus to the posterior horns of the spinal cord and hence analgesia. Such a procedure has been used successfully to treat phantom limb pain and some of the more severe back and peripheral ischaemic pains [2, 3, 6, 29, 54]. Severe angina pectoris also has been shown to respond to such manoeuvres [39]. The stereotactic application of electrodes to the thalamus, mid-brain and medulla is reserved for a highly selected group of patients with severe, unresponsive, disabling pain [47]. The long term results and cost effectiveness of such procedures have yet to be evaluated fully. Their supplantation by cellular implant techniques may be the next major advance in this area.

Destructive lesioning

Thermal coagulation of the dorsal root ganglia of the cord is used to treat pain in the distribution of spinal sensory nerves [40]. However, in the light of the published success of Hakanson in treating trigeminal neuralgia with retrogasserian glycerine injections [22], a similar technique to invest the dorsal root ganglion of the spine with glycerine has proved just as beneficial [9]. The procedure is swift and can be performed on an out-patient basis.

Patients who have suffered traumatic avulsion of a brachial plexus frequently suffer severe pain in the useless limb, the amputation of which in no way alleviates the pain. Nashold has used thermal coagulation of the dorsal root entry zone of the cord in the avulsed segments (DREZ lesions) to produce good analgesia [41]. Whilst late results are acceptable [55] the early use of transcutaneous electrical neural stimulation (TENS) may well obviate the need for major surgical intervention before the making of the DREZ lesion [6].

Cryotherapy has never achieved its full potential as a neurolytic technique, although its value has been shown in the periphery and centrally, particularly in displacing the use of intra-pituitary alcohol injection for disseminated malignant disease [18]. Its recent use in pituitary ablation for the treatment of non-cancer pain is both successful and debatable, but may indicate a novel line of therapy for the future in some of the more recalcitrant problems [20].

CONCLUSION

The treatment of chronic pain is one of the most complex in medical practice, embracing the whole of conventional medicine and encompassing much of basic science and complementary medicine. It is unlikely that the future will bring a panacea with which to treat all types of pain, whatever their cause, but more likely that co-operation between the clinician and the researcher will produce logical leads for both to follow. Psychological evaluation and therapy will maintain its importance and data collection will provide a valuable guide to the development of treatment and service.

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OPIOIDS IN CHRONIC PAIN

H. J. McQUAY

SITE AND MECHANISM OF ACTION

The aim in using opioid drugs in chronic pain is optimal pain relief with a minimum of side effects. A rational approach requires understanding of the clinical pharmacology of opioids given by a variety of routes, for the differences between routes may be greater than the differences between drugs given by the same route. Those using opioids in chronic pain differentiate between their clinical and laboratory pharmacology, a distinction which is not so apparent in acute, operative and postoperative care. The side effects which are perceived as limiting clinical use, such as respiratory depression and dependence liability, are often of minimal clinical importance in chronic use, as long as appropriate doses are used to treat opioid-sensitive pain.

Opioid Receptors

Opioid drugs work as analgesics by binding at opioid receptors in brain and spinal cord. A schematic view of the relationships between the mu, delta and kappa receptor subgroups is shown in figure 1.

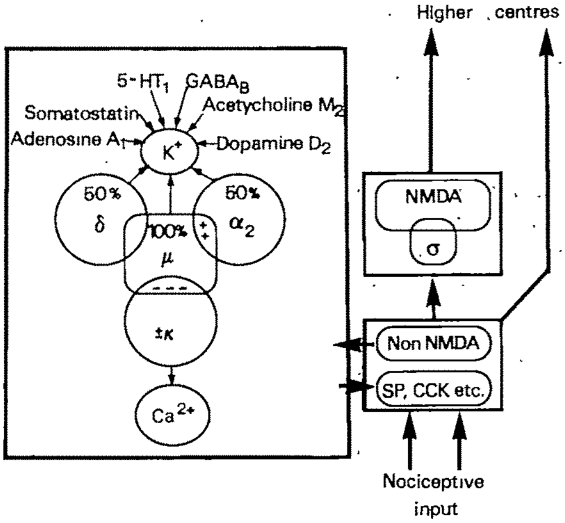

FIG. 1. Relationships between receptor subtypes. The major opioid receptor subtypes are mu, delta and kappa. Sigma receptors associated with the N-methyl-D-aspartate ion channel do not meet all the criteria for true opioid receptors, but are capable of providing analgesia. Delta and mu may coexist in the same cell; kappa does not co-exist with mu or delta [47]. The mechanisms by which they achieve their effect also appear to be different, mu and delta operating through the potassium channel, kappa via the calcium. Kappa shifts the mu dose response to the right, and this is shown by — in the figure. The relative ability of ligands for the subtypes to achieve maximal analgesia on the dose–response measures is shown by the percentage figures in each section: mu 100%, delta ?50% etc.

Exogenous opioids used in pain management have different binding selectivities on the different receptor subtypes. The functional role of these different endogenous systems is unclear. The mu system has an analgesic effect in both acute and chronic pain, although the endogenous ligand is unknown in certain areas. Enkephalins appear to be the endogenous ligands at delta receptors and blocking the degradation of enkephalins produces analgesia in animal pain models [15]. The kappa system is more enigmatic. In animal models of chronic pain increased quantities of dynorphin, the endogenous ligand, are found in the spinal cord. The relevance of this to analgesic activity is unclear because in behavioural studies direct cord application of kappa ligands does not produce analgesia in all test systems, although effects are seen with systemic administration [32]. Electrophysiological studies with intrathecal doses revealed two types of kappa effect, one decreasing C fibre firing, the other increasing it; the net result was no analgesia [30]. The kappa system may establish the baseline activity on which mu and delta operate. This may be important in chronic pain states.

Two strategies for future development of analgesics were proposed as a result of receptor identification. The first was that analgesia without

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side effects might be achieved by use of kappa- or delta-selective drugs. This has yet to be proved clinically. The second was that blocking the degradation of enkephalins might produce analgesia, again without side effects, because an endogenous analgesic was being made to last longer. Blocking degradation is effective in animal models, although the maximum analgesic effect may be considerably less than that achieved by mu agonists [15].

Animal models of chronic pain suggest that the N-methyl-D-aspartate (NMDA) receptors may also be important. Specific NMDA antagonists produce analgesia, as do opioids with anticonvulsant actions [72]. Coherent strategies for future opioid analgesic development for chronic pain may need to focus on this site, because those chronic pains which respond poorly to opioids (see below) are sometimes responsive to anticonvulsant and antidepressant drugs.

Conundrums in Opioid Clinical Pharmacology

The clinical pharmacology of the opioids has some important differences from the effects observed in the laboratory. These differences appear to depend on the presence or absence of opioid sensitive pain when the drug is given. In the presence of such pain, appropriate doses do not lead to the problems of respiratory depression and addiction. These are the two commonest reasons given for limiting prescription, so that understanding of this "dual" pharmacology is of more than just theoretical interest, especially in regard to pain conditions which respond poorly to opioids.

Respiratory depression

It is easy to demonstrate the respiratory depressant effect of agonist drugs in volunteers. In patients with pain, however, clinically important respiratory depression is a rare problem, both after operation and in chronic pain states [69]. The mechanism by which the presence of opioid sensitive pain *protects* against the respiratory depressant effect is unknown, but is important clinically. Taking a double dose of morphine at night does not cause problems [56], but patients adequately treated with opioids develop respiratory depression if the pain is taken away by a nerve block and the opioid dose is not decreased [22, 35]. The balance between nociceptive input and opioid effect is necessary to avoid respiratory depression. After successful nerve blocks, opioid dosage should be decreased by 75%; further reduction may then be possible over the following weeks.

The mechanism of this balance may be more specific than arousal, which was the explanation given for the phenomenon of greater respiratory effects of opioids in anaesthetized volunteers [19]. Medullary respiratory centre cells with nociceptive input have been demonstrated in the cat [1], and input here may act to balance the respiratory depressant action.

Concern about respiratory depression should not inhibit the appropriate use of opioids, which is to provide analgesia when the pain may reasonably be thought to be sensitive. The corollary is that, when opioids are used for insensitive pain, or in sensitive pain at doses greater than those required for analgesia (as in the ITU to facilitate ventilation of the lungs), or for purposes other than analgesia, such as sedation, then the problem of respiratory depression may be encountered.

Opioid-insensitive pain

In chronic pain it has long been realized that not all pain states are relieved by opioids [34]. A good example is trigeminal neuralgia, in which they provide poor pain relief and the anticonvulsant, carbamazepine, works well. Opioid sensitive pain may be defined as pain which responds progressively to increasingly potent drugs: the corollary is that opioid insensitive pain does not. This distinction is shown by the failure of some patients with chronic pain to distinguish the analgesic effect of i.v. drugs from placebo [3].

Arner and Meyerson [3] assessed the opioid sensitivity in three groups of chronic pain patients: those with "primary nociceptive pain", those with "neuropathic deafferentation" and those with "idiopathic pain" (little or no demonstrable pathology). Effective relief in nociceptive pain contrasted with lack of response in the other two groups. The paper emphasized the clinical necessity of distinguishing between pathological pain conditions rather than considering them as homogeneous and assuming that the response to opioid treatment will be the same [8].

The commonest causes of opioid insensitive pain are nerve compression and nerve destruction (deafferentation) and the reason may be loss of primary afferent receptors with post-synaptic preservation. The deafferentation pain associated with nerve destruction in cancer patients usually results from tumour infiltrating the nerve. The painful area may have decreased or altered sensation. An analogous (and also opioid insensitive) pain is seen in post-herpetic neuralgia. Nerve compression may produce a neuralgic pain, often not controlled by opioids, in an area with normal sensation. Other causes of opioid insensitive pain include gastric distension, rectal tenesmoid pain and central pain (thalamic pain; phantom limb pain).

The clinical difficulty lies in patients with pain at more than one site (when that at one site is sensitive and the other is not) or in distinguishing a dose response for mood elevation from one for analgesia. Relative opioid insensitivity may be predicted from history and examination. Management may be pharmacological, with unconventional analgesics (antidepressants, anticonvulsants or steroids [34]), or with nerve block or surgery.

Addiction

The fear of producing addiction is, together with respiratory depression, one of the main reasons for underuse of opioids in treating chronic pain. Addiction, the "...*compulsion to take the drug on a continuous or periodic basis in order to avoid the discomfort of its absence*" [73], is, like respiratory depression and tolerance, a facet of opioid pharmacology which is rarely a clinical problem.

To determine the incidence of opioid addiction, the Boston Collaborative Drug Surveillance Programme examined the files of nearly 12000 medical inpatients who had received therapeutic opioids. There were only four clear cases of dependence in patients with no previous history of addiction [54]. Such psychological dependence should be distinguished from physical dependence; in the context of successful nerve block the opioid dose may be decreased dramatically, and withdrawal symptoms and signs may follow [29], as can happen in intensive care.

The other complicating factor is the political assumption that medical availability of opioids necessarily increases street addiction. While drug supplies may go astray and be used by street addicts, patients who are prescribed opioids for the management of sensitive pain do not become addicts. To deprive them of this means of pain relief is unjust.

Tolerance

Tolerance may be defined as the need for a larger dose (or greater plasma concentration) to achieve the same pharmacological effect. The word is often misused in pain management to mean an increase in dose; this is only correct if the pain has not increased, and in chronic cancer pain the reason for increasing the dose is usually an increase in the pain [29]. Patients are often maintained satisfactorily on the same oral dose of morphine for months, and this would not be possible if tolerance always occurred.

Genuine tolerance does occur in other contexts. Addicts develop tolerance because they are using opioids in the absence of pain. Acute tolerance has been demonstrated in animal studies: control groups given a painful stimulus before the injection of opioid did not develop acute tolerance [10]. The phenomenon of acute tolerance has also been demonstrated in man [36]. Opioid injection before surgery (before the patient is in pain) is common practice, both as premedication and in the anaesthetic room. It does not create clinical problems because any increase in postoperative drug requirement can be met.

Tolerance to spinal opioid has caused clinical problems in chronic pain management but many of the reports are hard to interpret. In some cases spinal opioids were used for pain which had failed to respond to opioids given by conventional routes. On the basis of this and other clinical criteria, these were opioid insensitive conditions. The second problem with interpretation is in knowing whether the dose being given was the minimum necessary or was more than was needed. If the latter, tolerance would be expected.

The enigma of opioid tolerance reinforces the concept of a dual pharmacology. When the drugs are used in appropriate doses to treat pain which is sensitive, tolerance (like respiratory depression) is not a clinical problem. When opioids are used in the absence of sensitive pain, or in inappropriately high dose when the pain is sensitive, then (like respiratory depression) tolerance can occur.

Indications for Treatment

Patients are often referred to a pain clinic because of failure of conventional analgesic regimens, or because the referring doctor is unwilling to use the dose necessary to achieve analgesia. The use of opioid drugs is only one of the possible approaches (fig. 2) and the first issue in deciding if they are

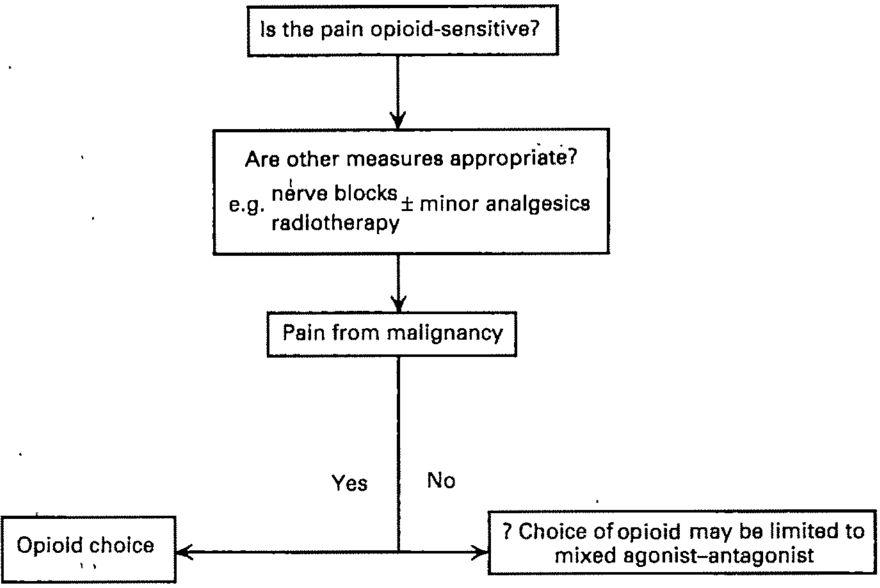
Is the pain opioid-sensitive?
Are other measures appropriate?
e.g. nerve blocks ± minor analgesics
radiotherapy
Pain from malignancy
Yes
No
Opioid choice
? Choice of opioid may be limited to mixed agonist–antagonist

FIG. 2. Opioids as one possible approach in chronic pain.

appropriate is that of the sensitivity of the pain (see above). There is little logic in using opioids to treat a pain which does not show a clear dose–response relationship.

Opioids in non-malignant pain

The second issue is that using opioids in non-malignant pain is contentious. The arguments against include the problems of addiction and dependence and the potential long term adverse effects [61]. While there is little evidence to show that these are major risks [18, 53, 64], there are few advocates for the argument that long-term use in such conditions is ideal. The problem remains however, that it may be the only effective remedy. In the small number of patients for whom this is the case, the prescriber should ask two questions: "Is the pain sensitive?", and "Is there no other effective remedy?". If the answer to both questions is yes, then the position must be explained to the patient, the family practitioner and the others involved in the patient's care. The use of drugs such as the partial agonist buprenorphine may be more socially acceptable for this patient group because of the perceived lower dependence liability.

CURRENT PROBLEMS

In addition to tolerance, some of the unresolved clinical issues are the choice of opioid, the decision to prescribe by the clock or as required, and choice of route [18].

Choosing an Opioid

While morphine remains the standard against which others are judged, other drugs may act faster, last longer or have a better balance between effect and side effect for a particular patient. Factors involved in choice of opioid thus include:

Efficacy and ceiling effect
Speed of onset and duration of action
Side effects
Agonist *v.* mixed agonist–antagonist
Prescriber (or institution) preference

It is easy to forget that morphine is not available in many countries of the world because of the political decision that medical availability increases "street" availability. Knowledge of the alternatives is then a necessity. Mixed agonist–antagonists have particular importance in this context because they have lower dependence liability and may be the only permissible agents. For the same reason choice may be limited to this group in non-malignant pain. Drug availability and prescriber or institution preference may thus be the most important determinants of choice.

Efficacy and ceiling effect

When treating chronic pain it is always possible that the pain will increase as the disease progresses. This affects the choice of drug, because it can be argued that there is no point in prescribing initially an agent which will be incapable of relieving severe pain if the situation deteriorates. The argument is not wholly consistent, because progressive prescribing from non-opioid to opioid is a legitimate strategy, but it highlights the problem of the ceiling to analgesic effect. This is the inability of a drug to relieve pain beyond a certain intensity, despite an increase in dose. One reason that oral morphine has become the standard strong oral analgesic for continuous treatment in cancer pain [66] is that it is effective (with no apparent ceiling) while being relatively safe.

Three types of analgesic ceiling may be distinguished: that from toxicity at higher doses, ceiling as an intrinsic drug property and ceiling from a failure of compliance.

Toxicity. If increasing the dose increases the incidence of unwanted effects, this creates a limit to analgesic efficacy. Codeine and dihydrocodeine are usually classified as "weak" analgesics occupying an intermediate rung on the analgesic ladder. They are inadequate at the greater doses required to control severe pain because of the unacceptable side effects produced with such doses. Similarly, pethidine in large doses (oral doses of 200–300 mg 3 hourly, see below) produces central nervous system toxicity.

Intrinsic drug property. Drugs acting as partial rather than pure agonists may be incapable of relieving severe pain. This may be more of a theoretical than a practical bar to use, because the ceiling effect may occur only at high doses. However, this worry together with fear of negative interaction with pure agonists, has limited the use of mixed agonist–antagonists (see below) in cancer pain.

Failure of compliance. If the dose of drug in each tablet (or ml of solution) is small, and the dose required is large, it may be physically difficult for the patient to take the necessary dose.

Speed of onset and duration of action

Fast onset of effect is not a critical factor if the patient is receiving regular medication, but may be relevant for the patient taking a drug according to need. Several drugs have faster onset times than morphine (table I).

Alternative oral opioids might also be said to have advantages over morphine if their analgesic effect lasted longer, because fewer doses would be needed each day. At least three alternatives do last longer than morphine. The long plasma half-life of methadone after a single dose (table I) is out of step with the duration of its analgesic effect, so that it is more difficult than morphine to use effectively and safely. There has been a great deal of confusion because of the disparity between the effect half-life and the kinetic half-life, for methadone and for other drugs. Patient self-titration with methadone is one method to achieve safe use [59]. Levorphanol also has a long plasma half-life (12–16 h), and an analgesic effect duration of 8 h. Buprenorphine has a duration of effect of 8 h, but is a partial agonist. However, the advent of sustained release formulations of morphine means that there is now less reason for choosing another opioid on the grounds of longer duration of effect.

Sustained release formulations. Although the drugs with longer kinetic half-life such as methadone can be titrated safely by patients [59], the

TABLE I. *Onset time, time of peak effect, half-life and duration of relief with opioid drugs.* (*Adapted from* [65])

	Onset (min)	Peak (min)	$T_{\frac{1}{2}}^{\beta}$ (h)	Duration of relief (h)
Dextromoramide	10–20	60–90	?	2
Pethidine	40–60	60–120	2.5	2
Morphine	60	60–90	3	4
Nalbuphine	15–30	45–60	?5	4
Levorphanol	20–60	60–120	12–16	6
Phenazocine	20	45–60	?	6
Dipipanone	45–60	90–120	?	6
Buprenorphine	60–120	120–240	3.5	8
Methadone	30–60	30–120	15/48	8
MST	120	180+	(3)	12

only real advantage appears to be fewer daily doses than with morphine in solution, and effectively a fixed dose schedule still operates. This advantage has been minimized with the advent of sustained release formulations of morphine which also decrease the number of doses required daily. These preparations are formulated to release morphine over a prolonged period (12 h). Clinical experience and controlled studies have both shown that twice daily dosage substitutes for the same total daily dose of morphine sulphate solution taken 4-hourly, and for many patients twice daily doses are more convenient. One disadvantage is that the time to maximum plasma morphine concentration is longer than is found with oral morphine sulphate solution (approximately 4 h compared with 1–2 h).

Specific side-effects and metabolism

If an opioid has no specific advantage over morphine and has a specific disadvantage, such as a troublesome side-effect not found with morphine, then there is little logic in choosing that drug in preference to morphine. Given equivalent analgesic potency, any drug which produced fewer side effects than oral morphine would be an improvement. For most clinically important side effects such as constipation or nausea, there is no comparative evidence from chronic pain patients to suggest that any of the alternatives produces fewer side effects while providing equivalent analgesia. The evidence from single-dose post-operative studies shows a higher incidence of nausea and vomiting with pethidine [45], and dysphoria (see below) with those mixed agonist–antagonists which have a relatively high affinity for kappa and sigma receptors [68].

Dysphoria. This occurs with all opioids, but the incidence varies widely between drugs. There is little sense in using one which produces a higher incidence of dysphoria than morphine without any compensating advantage. Pentazocine, butorphanol and nalbuphine have this potential [24]. The greater than 20% incidence seen with pentazocine and butorphanol contrasts sharply with the 3% incidence seen with other opioids; drugs which produce this high incidence have no place in the management of chronic pain.

Toxic metabolites. Pethidine is metabolized to norpethidine, which is toxic [63]. It causes unwanted CNS changes, tremor, twitching, agitation and convulsions, and the incidence of these problems increases considerably at doses above 200–300 mg, and in the presence of impared renal function [7, 63]. Together with its short duration of action (2–3 h (table I)), this makes pethidine a poor choice for the management of chronic pain.

Active metabolites. Recent work on diamorphine, on the metabolites of morphine and on the method of excretion has some important clinical implications. Of the drugs shown in figure 3, diamorphine [28] and morphine-3-glucuronide (M3G) [9] do not bind to opioid receptors, whereas 6-monoacetylmorphine, morphine, morphine-6-glucuronide (M6G) and normorphine do. Quantitatively, the most important active metabolite is M6G, because M3G and M6G are the major metabolites of morphine in man [6, 58] and because of the greater potency of M6G compared with morphine. In rats, M6G is 45 times more potent than morphine intracerebrally and nearly four times more potent subcutaneously [60]; intrathecal injection gave potency ratios between 10 and 20 [62]. M6G may contribute substantially to the analgesic effect of morphine, in both single and repeated doses [20, 39, 50].

Diamorphine is a classical "pro-drug". Devoid of analgesic activity itself, it initiates the "cascade" into the active 6-monoacetylmorphine, morphine and M6G (fig. 3). Because of the speed of these reactions, there is no clinical advantage over morphine by oral or i.m. routes, in terms either of greater analgesic efficacy or of improved mood [28, 67]. This does not exclude advantage from i.v., spinal or other routes.

The major advantage of diamorphine over morphine is solubility. This is relevant when injections of large doses are necessary, because they can be given in a small volume. This may also make diamorphine a logical choice when large doses are necessary for subcutaneous infusion.

Renal function

Unexpected degree and duration of effect can be obtained with morphine and its congeners when they are used in patients with severely impaired renal function [37]. Cumulation of M6G is the probable explanation for this phenomenon. Prolonged respiratory depression has been reported in man in association with negligible plasma concentrations of morphine, but with very high concentrations of M3G and M6G [49]. The relevance of this problem to chronic pain man-

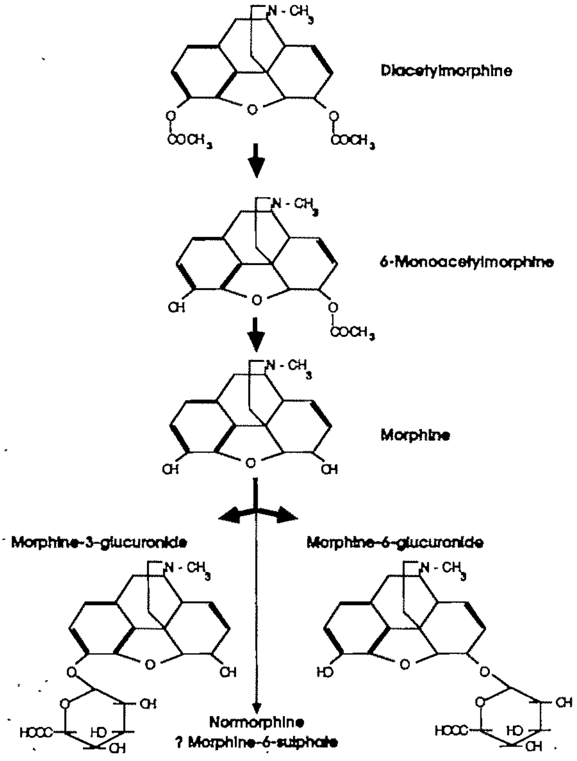

FIG. 3. Diamorphine, morphine and metabolites.

agement was shown by decreased oral morphine requirement in patients with impaired renal function [57]. These patients (plasma creatinine concentration > 180 µmol litre^{-1}) required smaller doses (5 mg, 4 hourly) than the median (20 mg, 4 hourly).

Problems should arise only if a fixed-dose schedule is used without taking account of renal function, or without adequate titration against pain intensity. Drug doses should be decreased markedly if creatinine clearance is less than 30 ml min^{-1}. With less severe renal dysfunction the potential problem emphasizes the need for careful titration, remembering that renal function deteriorates with advancing age.

Hepatic function

Glucuronidation of morphine is altered little in hepatic failure [52]. Patients require the same morphine dose as those with normal hepatic function [31, 57]; the mechanism of the problems encountered in hepatic pre-coma is not known [31], but may be as much dynamic as kinetic.

Dose equivalence

When changing between the oral and the parenteral route, the dose of morphine must be adjusted, but the exact ratio for the change is not known. In one study the effect of a single injected dose was six times that of an oral dose [25]. In the multiple dosing context of chronic pain, ratios of 2:1 or 3:1 are used successfully [66].

The discrepancy between a ratio of 1:6 with single doses for acute pain and 1:2 or 1:3 with repeated doses for chronic pain has led to much confusion. Both are correct within their clinical contexts. The explanation for the discrepancy may be that active metabolites contribute more to the analgesic effect with repeated doses than with a single dose [21, 39]. An important clinical point is that patients differ, both in the bioavailability of oral morphine (15–64 %, mean 38 % [58]), and in the effect of the drug, so that individual titration is necessary.

Mixed Agonist–Antagonists

These drugs combine the ability to act like morphine (agonist activity) with potential antagonist activity. Common to the group are lower dependence liability than is found with agonists and a ceiling to their efficacy.

These properties come from the presumed activity of these drugs on more than one opioid receptor type. The simplest (and clinically most important) way of classifying these drugs is into those which are morphine-like, because of partial agonist activity at the mu receptor (buprenorphine), and those which are more similar to nalorphine (pentazocine, butorphanol, nalbuphine), with agonist action on the kappa receptor. The classification is clinically important because, whereas morphine-type drugs predictably have subjective and physiological effects like morphine, and do not cause a higher incidence of psychotomimetic reactions than morphine, the nalorphine-type of mixed agonist–antagonists cause increased incidence of psychotomimetic reactions (see above) and this limits their usefulness in chronic pain.

The ability of these drugs to antagonize other opioids has led to the dictum that they should not be prescribed together with agonists. This antagonist ability is, however, far from straightforward, first because antagonism is more evident with chronic exposure [27], and second because many patients who have been prescribed both agonist and partial agonist drugs at doses within the "normal" therapeutic range, appear to have additive analgesia [33]. While co-prescription makes little sense, because it invites problems unnecessarily, the disparity between the clinical observations and the pharmacological predictions remains to be explained satisfactorily.

The issue of ceiling to efficacy appears to be restrictive in chronic pain only for nalbuphine (ceiling equivalent to morphine 30 mg); for buprenorphine the ceiling has been estimated at 5 mg day^{-1} [77], at which point compliance is more likely to be a limiting factor. Two benefits of efficacy ceilings are that the ceiling for respiratory depression appears to be equivalent to approximately 20–30 mg of morphine, making the drugs theoretically safe in overdosage. Theoretically there should also be a ceiling to constipation.

Prescribe Regularly or as Required?

Should opioids be given on a fixed "by the clock" schedule or when the patient asks for them? The rationale for the safe and effective hospice teaching that the fixed dose schedule for oral morphine is best is that such schedules prevent the pain re-emerging. If this is allowed to occur, the relatively slow onset of analgesic effect of oral morphine means that it takes time to re-establish control. Sustained release morphine formulations may have an even slower onset time, and hence be even more ineffective.

While there is no inherent merit in allowing the pain to re-emerge in this way, some patients feel "drugged" when taking oral morphine on a fixed dose schedule, and would prefer to take the drugs when needed. Others require additional rapid onset pain relief for pain which breaks through background analgesia. Unfortunately, the kinetic and dynamic profiles of the alternative oral opioids do not offer much advance over oral morphine. Faster onset of analgesic effect is required for on-demand use, and this is claimed for dextromoramide and levorphanol (table I), and for morphine hydrochloride compared with morphine sulphate. A regimen may be tailored with background control with morphine and a faster onset oral opioid in addition, either to enable patients to titrate their pain relief against any clouding of thought or to control unpredictable break-through pain.

Alternatively, judicious use of non-steroidal anti-inflammatory drugs or paracetamol may be used to get round this problem, adhering then to the purist philosophy of only prescribing one opioid at a time. Combining the effects of aspirin and opioid produces an additive increase in analgesia [26], known as the opioid-sparing effect because greater analgesia is achieved without increasing the opioid dose.

Route of Administration

Thirty years ago many doctors did not believe that oral opioids were effective analgesics, despite centuries of use. Now that the oral route is the accepted standard for chronic cancer pain, novel routes are being explored to improve pain relief and to minimize side effects.

Two clinical issues have become confused in discussion of alternative routes. The first is *clinical necessity*; some patients may *have* to be managed by a "non-standard" route of administration, such as those cancer pain patients who cannot take oral medication. The overall proportion of patients in this category is not known, but is likely to be greater in a pain clinic or hospice because referral will follow failed oral treatment. The second is the *potential* of novel routes to provide better analgesia or fewer side effects than standard routes, so that the novel route supplants the standard. The current problem is providing cogent clinical evidence to confirm these potential benefits [16].

The sublingual and spinal routes are discussed in some detail because they are current clinical alternatives to conventional routes of administration. Other proposed routes (nasal, transdermal, inhalation, etc.) should be subject to the same questions: what is the kinetic logic of the route, and what is the clinical logic?

Sublingual and buccal opioids

Kinetic logic. The kinetic logic behind using the sublingual and buccal routes is that the drug is given without injection, but is absorbed systemically (analogous to an i.m. dose), avoiding any first-pass effect. Circumventing this increases relative systemic bioavailability, but the real clinical gain is that it should make the effect of a given dose more predictable both within and between patients than an equivalent oral dose. It is the variability of the first-pass effect which makes short-term use of oral opioids difficult. An additional gain of faster onset of analgesic effect was anticipated by analogy with other drug classes used sublingually (15 min for anti-angina drugs).

Sublingual buprenorphine provides the best example of the kinetic gain in availability. After operation, 0.4 mg sublingually produced analgesia equivalent to that obtained with 0.3 mg i.m. Relative systemic availability was 55% (range 16–94%). The relative systemic availability of oral buprenorphine, in contrast, was about 15% [38, 71]. Substantial gains in onset time for analgesic effect have not been found; 30 min is the accepted time in chronic use.

The kinetic advantage of sublingual use would be predicted for high clearance drugs with a substantial first pass effect when taken orally, but not for low clearance drugs. No advantage for sublingual use of methadone, which has a low clearance and high oral availability, would be expected and none was found [38]. Similarly little kinetic advantage was found with sublingual morphine [38, 51, 71], and recent work with buccal morphine [4] had no oral controls, so that no advantage over oral relative systemic availability could be shown.

Little is known about the influence of formulation and physico-chemical properties of drugs, such as lipophilicity, on sublingual and buccal availability. Manipulating the drug formulation may maximize the availability and minimize problems of taste and local irritation; it will not change the logic that avoiding the first-pass effect is an advantage only for high clearance drugs which are subject to a substantial first-pass effect. Such manipulation might also result in a faster increase in plasma concentrations and hence produce faster onset of analgesic effect; this advantage would apply to both high and low clearance drugs.

Clinical logic. Sublingual use is an alternative for patients in whom swallowing is difficult, and when a drug can produce analgesia as good as could be achieved by injection. Sublingual buprenorphine produces analgesia equivalent to parenteral doses. This advantage should be considered particularly when potent opioids are needed in contexts where injection is most problematic: in children, in subjects with haemophilia or in patients who cannot swallow. The agonist drug phenazocine has also been used sublingually [5], but there are no comparisons with the use of oral morphine.

Subcutaneous injection

Injection of opioids is necessary when a patient cannot swallow medication, cannot absorb it or has persistent vomiting. The choice of drug for parenteral use may be dictated by consideration of the volume to be injected, particularly if repeated injections have to be given in cachectic patients. Diamorphine is much more soluble than morphine (100 mg will dissolve in 0.2 ml) and is used widely in Britain for this purpose. The dose given for injection is half the orally effective dose of diamorphine (30% of the orally effective dose of morphine). Morphine acetate and hydromorphone hydrochloride are alternatives.

Subcutaneous infusions using a battery-driven portable syringe driver [48] may be useful for the patients (e.g. those with inoperable bowel obstruction) who need longer term parenteral medication.

Intravenous use

Hospitalized patients and those with long-term central venous cannulae may be managed with i.v. bolus or infusion, and the route has been used successfully in the young [42, 43].

Spinal Opioids

Giving opioids by spinal (a generic term for intrathecal and extradural) routes in chronic pain management is contentious, for it has potentially greater morbidity than conventional routes. The importance of spinal opioids is the potential for a quality and duration of pain relief greater than that achieved with conventional routes. This potential puts spinal opioid use in the category of novel routes for which the risk:benefit ratio compared with conventional routes must be defined [16]. The belief that applying opioid directly into central nervous system (CNS) produces an absolute difference in incidence of analgesia and side effects compared with conventional routes has little logic behind it; the drugs act on the same receptors however they are given, so that the difference can be only relative. Spinal opioid use in chronic pain has had a strong phenomenological flavour. The appropriate clinical role is not resolved.

Kinetic logic

Spinal administration uses injection of exogenous neurotransmitters close to the CNS to work directly on the receptors. The kinetic problems of conventional routes, such as uncertain absorption into, and delivery by the circulation to, CNS sites, are hence circumvented. The process, however, substitutes a different set of problems. The principles which underlie the systemic kinetic differences between drugs, such as the influence of lipophilicity on the ability to cross the blood–brain barrier [23], are circumvented by direct spinal application [40]. This is evident in the potency of different mu agonists given i.v. or intrathecally. Methadone 10 mg given systemically produces analgesia equivalent to that from systemic morphine 10 mg. Intrathecally, however, the ED_{50} for methadone is 18 times that of morphine [40]. These differences between systemic and spinal dose requirements have not been applied as they should have been in determining equianalgesic doses.

The benefit of giving opioid extradurally as opposed to using conventional parenteral routes comes from the fraction of the extradural dose which crosses the dura directly. While the kinetics of this fraction will be predictable from intrathecal kinetics, the proportion of drug absorbed systemically will follow the kinetic principles for systemic absorption. Taking the example of methadone, the "systemic" fraction is equipotent with morphine, but the "spinal" fraction is not, because of lipophilicity. This additional complexity has not been addressed adequately.

The high drug concentrations achieved after lumbar intrathecal injection [44] spread rostrally [46], and make a combination of spinal and supraspinal effect possible. This may be a necessary combination for adequate analgesia. Systemic absorption from the extradural space would also take drug to supraspinal receptors. The high CSF concentrations, however, also raise the spectre of toxicity, which may be of particular importance if spinal opioids are to be used in non-malignant pain. None has been found, either in prolonged studies in monkeys (4–16 months extradural morphine [75]), or in man after 6 months extradural morphine [41]. Both dural thickening after chronic intrathecal administration [12] and pain on extradural injection [76] are attributable to disease rather than to the spinal opioids. The use of the more potent agents should perhaps be recommended, on the basis of fewer non-specific actions, until more is known.

Clinical logic

Analgesia. For chronic pain there is evidence that a small dose of drug given spinally can provide analgesia equivalent to that from larger doses given orally or by conventional injection routes. The duration of effect of these smaller doses may also be greater. There is little comparative evidence for a lower incidence of side effects.

Opioids are often administered spinally in chronic pain when they have failed by conventional routes. This presumes that the failure is based on the drug not reaching the receptors in the CNS so that, if it is given directly, analgesia will ensue. Unfortunately, it is difficult to be sure from the literature that reports of success or of failure are reports of patients who fulfil this criterion. Overall, the proportion of patients for whom conventional routes fail is low (? 15 %), and the majority of these have pain at one or more relatively opioid-insensitive sites.

The crucial issue is whether or not the pain is sensitive, because there is no point in using opioids if it is not [2], and even less point in delivering them by a route which has a high morbidity. Sensitivity may be determined using the i.v. route [3], or by double-blind comparison between intrathecal opioid and saline [17]. Most sensitive pain can be managed successfully with oral administration, so the high morbidity spinal route is appropriate only if the pain is sensitive and conventional routes are contraindicated. The suspicion remains that spinal opioids can produce a better quality of analgesia with fewer side effects than conventional routes, but this is not proven. If this suspicion were to be confirmed, then the balance of the equation would be tipped in favour of more widespread use of the spinal route in patients managed currently with opioids given by conventional means.

A simple method of converting from the conventional route is to try 1 % of the total daily dose as the daily intrathecal dose, and 10 % as the extradural dose [11]. Initially, the intrathecal dose may be given once daily and the extradural dose twice. The doses used in chronic pain (0.05–1 mg [70]) may be increased as disease or tachyphylaxis develop [2]. There is no comparative evidence to recommend infusion rather than bolus administration, or to prefer constant infusion to systems with which additional demands can be met as in patient-controlled analgesia. Efficacy of low dose extradural infusions [14] suggests that the dose response for infusions may be different (response at lower doses) from that for bolus injection. If, at these low doses, the same quality of analgesia is provided with fewer side effects, infusion may be preferable. It is unclear whether or not the same is true for intrathecal administration. The overriding principle is to balance the dose and the pain. If infusions contravene this rule, the incidence of side effects is increased and tolerance will develop if a dose greater than that required for pain relief is given. If low dose infusion is preferable, the infusion must be "tailored" to the pain.

Intrathecal or extradural? The intrathecal route offers certain availability of the drug in CSF when compared with the extradural route. Spinal availability is a function of drug lipophilicity and there is variability between drugs. Technical difficulties with extradural injections and catheters cause variability between and within patients. There is an analogy to the certain availability of the i.v. route when compared with the i.m.

Intrathecal administration requires dural puncture, and the relative merits of repeated puncture against an intrathecal catheter [70] must be considered. The advantage of implantable intrathecal catheter systems is claimed to be a lower infection rate. The disadvantages are the extra logistic difficulty and the cost. Again, not all chronic pain is relieved by spinal opioids [2], and caution must be exercised before "leaping in" with an implanted system. Intraventricular catheters were used effectively for tuberculosis treatment and may have considerable advantage over long-term lumbar catheters, the usefulness of which may be limited by problems with CSF leakage and catheter maintenance [70].

An extradural catheter might be thought to have considerable logistic advantage and produce less morbidity than an intrathecal one, but there is no comparative evidence. The long-term (more than 1 year) use of extradural catheters in this context has been shown to be effective [13, 78], but with problems of obstruction, kinking, removal and infection. Tunnelling the catheter may reduce infection, but does not appear to reduce the incidence of the other complications [11]. The advantages of implanting injection reservoirs or systems remains to be seen. These "high-tech" approaches have often been used in patients with insensitive pain, making the results (other than logistic success) uninterpretable.

Side effects. The major problems encountered in acute pain are itch, urinary retention and respiratory depression. In chronic pain these have not been problematical [11]. The reason is not that chronic pain *per se* protects against these phenomena, but rather that previous opioid exposure seems to minimize the incidence. Comparisons of the incidence of side effects of chronic oral and chronic spinal administration are lacking. Anecdotally, patients whose use of oral morphine was restricted by side effects have had analgesia without side effects when spinal opioids were used. Comparisons of the incidence of side effects with different opioids given chronically by spinal routes are also lacking. Both types of comparison will require equianalgesic doses to be established.

The development of tolerance to spinal opioids (that is the need for larger doses to obtain the same effect), has been seen often in the treatment of chronic pain. Tolerance developed faster when opioid was infused spinally than when bolus injections were made on demand [17], but the problem is not insuperable, because increasing the dose defeats the tolerance. Temporary abstention has the same effect, presumably related to the advent of new (previously unexposed) receptors. The reason that tolerance develops faster with infusion than does demand may be that infusion at higher than necessary dose predisposes to development of tolerance (see above).

PRACTICAL PRESCRIPTION OF ORAL ANALGESICS

Two concepts underlie the sequential use of analgesics, "by the ladder" and "by the clock" [74]. In chronic pain of increasing severity, analgesics of increasing strength are used sequentially—ascending the ladder. In acute pain weaker analgesics are used as the pain intensity decreases—descending the ladder.

The standard non-opioid analgesic is aspirin. Paracetamol may cause fewer side effects and prove equally effective, despite a lack of anti-inflammatory activity. Non-steroidal anti-inflammatory drugs are more powerful analgesics than either aspirin or paracetamol, and may become the first line treatment. The archetypal weak opioid is codeine, but the combination of dextropropoxyphene with paracetamol is preferred by many patients because of lower incidence of side effects, particularly constipation. The standard strong opioid is morphine.

The concept of regular "by the clock" administration was discussed above. For codeine and morphine ("normal" formulations) a 4 hourly regimen is optimal. A 6 hourly prescription may be satisfactory for levorphanol, phenazocine or methadone (table I).

The following guidelines are suggested:

Non-opioid and weak opioid. With mild or moderate pain, use a non-opioid initially. If relief is inadequate, add a weak opioid, and titrate the dose against effect. Simultaneous prescription of two weak opioids makes no sense. If increasing the dose of the chosen drug does not relieve the pain, a strong opioid should be prescribed, rather than waste time by prescribing an alternative weak drug.

Strong opioid. Oral morphine should be used when the less potent drugs fail to control the pain despite regular use at an appropriate dose. The aim with opioid responsive pain is to titrate the dose of analgesic against the pain, increasing the dose appropriately until the patient is pain-free. The effective dose varies from patient to patient and from time to time; the correct dose for the patient is that which gives good pain relief for at least 4 h without unacceptable side effects. The range of morphine doses used is between 5 mg and 1000 mg 4 hourly, emphasizing the difference between patients; most never need more than 100 mg, and many need considerably less, the median 4 hourly dose of oral morphine sulphate solution being 10 mg [66].

The starting total daily dose of oral morphine for most patients whose medication is being changed from a weak opioid is 60 mg/24 h (10 mg aqueous formulation 4 hourly or 30 mg twice daily sustained release). The patient should be told from the start to take an extra dose ("escape" analgesic) if relief is inadequate. At the next assessment, these escape doses are added in to the calculation of total daily dose requirement, and the by the clock prescription is increased accordingly. If twice daily administration is preferable to 4 hourly, a sustained release formulation should be used. To convert the dose, the total daily oral dose (mg) is calculated and divided by two to give the sustained release dose in mg. However, adjusting the morphine dose can be difficult. It takes time (3 days) to judge whether the increase in dose has been effective, and small and ineffectual changes lose both time and the patient's confidence. The general rule is that the total oral daily dose is increased by 50%, from 60 mg/24 h to 90 mg, to 120 mg, to 180 mg, to 240 mg and to 360 mg.

Opioids should not be used without thought for constipation [55]. The use of anti-emetics as a routine is contentious. Initial nausea and drowsiness after commencing therapy with a strong opioid often decrease after about 3 days, and many patients never need an anti-emetic.

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Br. J. Anaesth. (1989), **63**, 227P–243P

PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

WARWICK MEETING

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MEASUREMENT OF RESPONSE TIME OF GAS ANALYSERS

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Knowledge of the response times of gas analysers is necessary when rapidly changing gas concentrations are being studied. Response times are usually quoted as T_{10-90}—the time taken for the signal to change from 10 to 90%. Previous work [1] has shown that the figure obtained for response time depends very much on the method of measurement.

We have designed and constructed a solenoid operated valve having a low resistance to gas flow (2 mm H_2O at 250 ml min^{-1}), small internal volume (55 µl), fast switching time (10–90% in 10 ms) and having symmetrical gas pathways.

Using this valve it was possible to calculate from the measured response time, and to verify experimentally, the response time needed to ensure that an analyser was capable of recording the end-expiratory (i.e. alveolar) concentration at any given rate of ventilation. However, to do this, assumptions must be made about the shape of the ventilatory wave form (e.g. an I:E ratio of 1:2). Conditions such as bronchospasm may invalidate such assumptions and introduce error.

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A METHOD OF MEASURING RATIO OF ENTRAINED TO INJECTED GAS DURING HIGH FREQUENCY JET VENTILATION

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Lung ventilation during high frequency jet ventilation depends on the volume of gas deliverd with each jet pulse, the volume of gas entrained, and the volume of gas "blown back" into the bias flow. At present, no satisfactory method exists for direct measurement of these volumes during HFJV, although tidal volume has been measured *in vitro* using a lung model [1]. We investigated a practical method for measuring the ratio of entrained to injected gas volume by integrating the gas flow obtained from differential airway pressure recordings.

In previous animal studies simple differential pressure measurements from within the lumen of the tracheal tube were utilized to produce gas flow curves, which could then be integrated [2]. A new method is based on measurement of flow between the bias flow tubing and tracheal tube using a pneumotachograph. Preliminary studies *in vivo* using this method enabled investigation of the variation of entrainment ratio with alteration of ventilation frequency, drive pressure and inspiration:expiration ratio settings on the high frequency jet ventilator.

Anaesthesia was induced with propofol, a neuromuscular

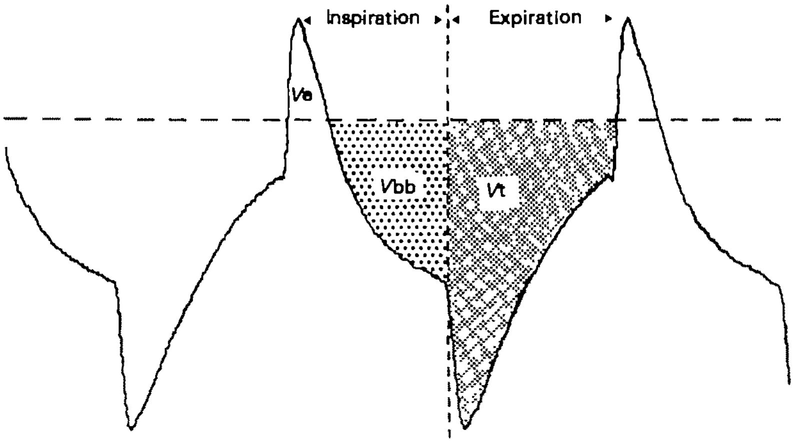

FIG. 1. Typical gas flow–time graph. *V*e = Volume of gas entrainment; *V*t = outward flow during expiration; *V*bb = outward flow during inspiration.

blocker was administered, and the trachea was intubated with a Mallinckrodt Hi-Lo jet tube. HFJV was applied using a Bromsgrove jet ventilator with a bias flow (1 litre min^{-1}), both supplying an $F\mathrm{I}_{\mathrm{O}_2}$ of 1.0. Maintenance of anaesthesia was with an i.v. infusion of propofol [3]. The patient's lungs were ventilated at five frequencies between 0.8 and 2.0 Hz, with I:E ratios of 0.1, 0.3 and 0.5. The driving pressure of the injected gas was 103.5 kPa.

A typical flow–time graph is shown in figure 1. Area *Ve* is a measure of the volume of gas entrainment, and represents the digitally integrated flow down the tracheal tube recorded by the pneumotachograph. Area *V*bb is the measured outward flow during inspiration and represents the "blow back" volume, and area *V*t is the outward flow during expiration and corresponds to tidal volume. The volume delivered by the jet is calculated as;

$$V\text{jet} = V\text{t} - V\text{e} + V\text{bb}$$

Expired and entrained minute ventilation increased with ventilatory frequency. Altering the I:E ratio from 0.1 to 0.3 increased the volume of gas entrained and increased inspiratory time, but a further increase to 0.5 considerably restricted entrainment as intrathoracic pressure increased. Entrainment ratio (*V*e/*V*t) was greater at low I:E ratios. "Blow back" minute volume decreases with ventilatory frequency and was always less at low I:E ratios.

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MEASUREMENT OF VENTILATORY INERTANCE BY PHASE ANGLE ANALYSIS DURING FORCED OSCILLATION

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BREATH-BY-BREATH EFFECTS OF INCREMENTS OF ALFENTANIL DURING SURGERY

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EFFECTS OF OPIOIDS ON THE PULMONARY CIRCULATION AND GAS EXCHANGE

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The purpose of the study was to investigate pulmonary haemodynamics and gas exchange after injection of eight different opioids.

After institutional approval and written informed consent, 58 patients scheduled for elective abdominal aortic surgery were allocated randomly to eight groups. All received diazepam 10 mg i.m. 45 min before investigation. After insertion of arterial and venous catheters, each patient received an opioid drug i.v. according to body weight:

Group I: buprenorphine 5 μg kg^{-1}
Group II: fentanyl 1.7 μg kg^{-1}
Group III: morphine 165 μg kg^{-1}
Group IV: nalbuphine 350 μg kg^{-1}
Group V: pentazocine 500 μg kg^{-1}
Group VI: pethidine 1650 μg kg^{-1}
Group VII: tramadol 1650 μg kg^{-1}
Group VIII: alfentanil 17 μg kg^{-1}

The doses assume an equianalgesic potency. A complete haemodynamic status and blood-gas analysis was obtained 10 min and 5 min before injection of the opioid and 5, 10, 15 and 20 min after injection.

Statistical analysis was by one- and two-way ANOVA.

Significant, clinically relevant increases MPAP and PVR were observed after injection of pethidine, pentazocine and buprenorphine. Pa_{CO_2} increased and Pa_{O_2} decreased following pethidine.

Opioids are known to cause respiratory depression, but additional factors such as histamine release and pulmonary shunt perfusion are likely to be involved in the changes in haemodynamic and respiratory behaviour observed. Possible adverse effects of pethidine [1] and pentazocine should be borne in mind during administration to patients with a compromized cardiovascular system [2].

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HAEMODYNAMIC RESPONSES TO INDUCTION WITH THIOPENTONE AND PROPOFOL MEASURED USING IMPEDANCE CARDIOGRAPHY

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The effects of various induction doses of propofol and thiopentone have been compared on heart rate (HR), mean arterial pressure (MAP), cardiac output (CO) and maximum rate of increase of aortic blood flow as measured by ejection velocity index (EVI). Measurements of CO and EVI were made using the non-invasive continuous cardiac output monitor (NCCOM3), which determines CO and EVI by measuring changes in thoracic electrical impedance (TEI). CO measurements obtained in this way have been shown to correlate well with those obtained using more invasive techniques [1].

The investigation was approved by the hospital Ethics Committee. Sixty unpremedicated ASA I patients (age 18–57 yr) scheduled for elective surgery were allocated randomly to six groups of 10 patients. Three groups received thiopentone 4, 5 or 6 mg kg^{-1}; the other three received propofol 2, 2.5 or 3 mg kg^{-1}.

Baseline measurements of CO, HR, EVI (NCCOM3) and MAP (Dinamap) were made before induction of anaesthesia and the induction agent was given over 20 s. Measurements were repeated at 1-min intervals for 10 min or until the patient showed signs of awakening. All the patients breathed oxygen through a Magill system. If they became apnoeic for more than 30 s, gentle manual ventilation was applied until spontaneous ventilation returned.

Both drugs caused increasing decline in CO with increasing dose. The maximum decrease in CO was greater after propofol than after thiopentone; however, the decrease in CO to its minimum value was more rapid with thiopentone.

EVI changed little with the two smaller doses of both agents, but the larger doses caused significant decreases in EVI. Thiopentone caused a slightly greater, non-significant decrease than propofol.

HR was greater in patients receiving thiopentone. More patients required manual ventilation after propofol than after thiopentone.

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ISOFLURANE DURING CARDIOPULMONARY BYPASS: EFFECT ON HAEMODYNAMIC VARIABLES

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ELECTROCARDIOGRAPHIC CHANGES AFTER SURGERY

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Various attempts have been made to quantify the risk of perioperative myocardial infarction. Early postoperative changes in the electrocardiogram (ECG) may occur in up to 19% of patients [1, 2].

Following Ethics Committee approval and informed consent, we studied the incidence of postoperative ECG changes and myocardial infarction (MI) in 210 patients (164 male) older than 40 yr (mean 70.6 (SD 10.9) yr) and undergoing elective surgery and anaesthesia. Demographic details, medical history, drug therapy, type of anaesthesia and surgery, and significant postoperative events or investigations were recorded. A standard 12-lead ECG recording was obtained before and on each day for 3 days after surgery. Postoperative changes were sought in rate, rhythm, conduction, mean frontal axis, QRS morphology, ST segments and T waves, according to criteria described by Rowlands [3].

TABLE I. *Numbers of patients with new postoperative ST/T wave changes.* (n = *No. in category*)

	No.	%
Overall ($n = 210$)	53	25.2
ASA I ($n = 88$)	14	15.9
ASA II ($n = 77$)	22	28.6
ASA III ($n = 45$)	17	37.8
Ischaemic heart disease ($n = 35$)	14	40.0
Treated hypertension ($n = 32$)	7	21.9

There were 87 patients with an abnormal preoperative ECG and these were older ($P < 0.001$) than those with a normal ECG. Overall, 60 patients developed changes in postoperative ECG, 53 to the ST/T segment (table I). New abnormalities were more likely to occur ($P < 0.001$) in those with an abnormal ECG before operation. Patients with a history of angina or a previous MI had a higher incidence ($P < 0.05$) of postoperative ST/T segment changes; this did not occur in patients with treated hypertension. The incidence of ST/T changes increased from ASA grade I to III ($P < 0.01$). The maximum incidence of ST/T segment changes was on the second day after operation (43 patients). Changes were present on all three days in 14 patients.

Three patients (1.4%) had ECG changes with symptoms and enzyme changes consistent with MI. These patients all presented with early postoperative hypotension or arrhythmia.

This study shows that ECG changes, especially of the ST/T segment, are common following anaesthesia and surgery and may be detected well into the postoperative period. Those with an abnormal ECG, a history of ischaemic heart disease, or ASA grade III may be more likely to show changes.

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A NEW FLUORINATED INHALATION ANAESTHETIC, I-653, IN VOLUNTEERS (PHASE 1 TRIAL)

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DRUG METABOLISM AFTER ANAESTHESIA

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Anaesthesia may alter the disposition of drugs [1, 2]. We have studied the effect of general anaesthesia which included halothane on the metabolism of paracetamol, which undergoes both conjugative and oxidative metabolism.

After obtaining informed written consent, we studied nine patients aged 18–50 yr undergoing minor elective surgery and nine healthy volunteers. All patients were ASA I and one was premedicted. Anaesthesia was induced with thiopentone 4 mg kg^{-1}, given with fentanyl 50 µg and maintained with 1–2%

TABLE II. *Percentage of total metabolite excreted in 24 h (median and range).* *$P < 0.05$, *Mann–Whitney test*

	Volunteers ($n = 9$)	Patients ($n = 9$)
Paracetamol (%)	2.9 (2.5–4.7)	2.0 (1.1–3.7)*
Sulphate (%)	24.3 (14.4–59.6)	22.2 (13.3–34.9)
Glucuronide (%)	65.9 (26.7–72.3)	64.6 (51.7–76.8)
Cysteine (%)	3.7 (3.2–4.0)	3.5 (3.2–4.7)
Mercapturic acid (%)	4.5 (2.9–7.9)	6.5 (4.4–9.6)*

halothane and 66% nitrous oxide in oxygen. Mean duration of anaesthesia was 21.5 min (SD 8.4).

Approximately 30 min after surgery, the patients were given paracetamol 1.5 g with 50 ml of water. Venous blood was collected at intervals for 12 h. The fasted volunteers received the same dose of paracetamol and had samples collected at the same times. Urine was collected at intervals for 24 h. Analysis of paracetamol in plasma and metabolites in urine was by HPLC [3]. Pharmacokinetic values were calculated using standard equations. Statistical analysis was by Student's *t* test or Mann–Whitney *U* test.

The groups did not differ significantly with respect to age, weight, sex, area under the plasma concentration–time curve, volume of distribution, half-life and plasma clearance.

The overall percentage of unchanged paracetamol excreted in 24 h was reduced and the percentage of mercapturic acid was increased in patients compared with controls ($P < 0.05$) (table II). The excretion of mercapturic acid was also increased ($P < 0.05$) in the periods 4–8, 8–12 and 12–24 h and the excretion of sulphate was reduced at 8–12 and 12–24 h ($P < 0.05$).

The increased excretion of the oxidative metabolite, mercapturic acid, after a short anaesthetic indicated a small but significant shift from conjugation to oxidation.

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EXPLICIT: AN INTERACTIVE PHARMACOKINETICS SIMULATOR FOR INJECTABLE ANAESTHETICS

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Most previous approaches to pharmacokinetic simulation have been based on the superposition principle. This has the disadvantage that frequent dose changes lead to greatly increased complexity of data management and manipulation. A computer based (IBM PC) interactive simulator has been developed which overcomes this complexity and permits both bolus and infusion dose changes, unrestricted as to timing and magnitude. Output can be obtained on a monitor, printer and plotter. The computational efficiency of the programme allows the simulation to run rapidly.

The mathematical technique used (matrix exponential) is one in which the continuous drug quantity–rate equations are written using intercompartmental microrate constants and the system reduced to matrix form [1]. This matrix is manipulated to obtain its equivalent for a discrete time step (e.g. 1 min) and can be used for sequences of bolus doses. Further manipulation produces an additional matrix which is used to simulate zero-order infusions [2]. These two matrices contain all the information required to simulate any combination of bolus and infusion, changes of dose being registered simply as input data; thus the 10th change of dose, for example, is handled as easily as the first. Concentration data for blood, representative of trends in compartment 1, are produced together with data for up to two other compartments. The technique has the flexibility to enable simulations for either very long periods (days) or very short periods (minutes) to be performed with the same accuracy; time steps in the range 0.1–10 min have been used. With a 1-min time-step, the simulation runs at about 100 times real time.

To validate the method, results obtained with a sequence of three bolus or infusion doses and with combined bolus and infusion schemes have been compared with those obtained by superposition. Results for all compartments agreed within 0.01%. Using representative pharmokinetic parameters derived from a three-compartment open mamillary model for propofol [3], the simulator can describe the blood concentration response for a variety of dose regimens. The programme is applicable to all drugs for which linear pharmacokinetics apply.

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ANTICONVULSANT PROPERTIES OF PROPOFOL: COMPARISON WITH THIOPENTONE

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INFLUENCE OF MORPHINE AND PETHIDINE ON THE INCIDENCE OF ANASTOMOTIC DEHISCENCE AFTER COLONIC SURGERY

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Painter suggested that, because morphine increases non-peristaltic contractility in the colon, producing segmentation and large increases in intraluminal pressure, it may be contraindicated in patients with a recent colonic anastomosis [1, 2]. Pethidine decreases colonic intraluminal pressure [2]. We compared the outcome of patients who received either pethidine or morphine for analgesia after construction of a colonic anastomosis.

Patients who presented for elective colonic surgery were allocated randomly to receive i.m. morphine (group M) or pethidine (group P) in the postoperative period. The anaesthetic technique was at the discretion of the anaesthetist, except for the use of i.v. opioid during operation. Anastomotic breakdown was assessed on clinical criteria; routine gastrograffin enema was not performed.

We studied 199 patients (group M: 47M/54F; group P: 50M/48F). There were no significant differences between groups in respect of age (M: mean 67.7 yr, range 24–88; P: mean 64.6 yr, range 19–91), grade of surgeon (M: 56 consultant; P: 55 consultant), method of bowel preparation, preoperative concentration of haemoglobin and plasma protein, colonic pathology, type of operation, selection of volatile anaesthetic agent or choice of neuromuscular blocker. Neostigmine was used in 86% of patients in group M and 88% of patients in group P. Patients received a mean total dose of morphine 67.5 (range 5–215) mg or pethidine 608.4 (range 100–2000) mg after operation in a mean of 7.4 (range 1–17) or 7.4 (range 2–22) doses, respectively.

Clinical evidence of anastomic breakdown occurred in 11 patients in group M and none in group P ($P = 0.003$); there was a suspected anastomotic breakdown, or radiological evidence alone, in another five patients in group M. Patients whose anastomosis broke down required significantly more blood (mean 2.5 units) than other patients (mean 0.96 units) and were discharged significantly later (mean 25.4 days *v.* 10.9 days). Of the 11 operations which resulted in clinical evidence of dehiscence, seven (64%) had been performed by a consultant surgeon, compared with 56% of other operations. Eight (73%) patients who suffered anastomotic dehiscence had received neostigmine, compared with 88% of other patients. Three patients died (two in group M, one in group P); one death was associated with clinically evident anastomotic breakdown, and one with suspected dehiscence.

We conclude that the incidence of anastomotic dehiscence after colonic surgery is greater when morphine is administered for postoperative analgesia than if pethidine is given. This is probably because of increased intraluminal pressures generated by morphine during the postoperative period, although a protective effect of pethidine cannot be excluded.

ACKNOWLEDGEMENT

This study was supported by a grant from Leicestershire District Health Authority.

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EFFECT OF METHIONINE ON IMPAIRED DNA SYNTHESIS DURING EXPOSURE TO NITROUS OXIDE

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Impairment of DNA synthesis by nitrous oxide is thought to result from inactivation of vitamin B_{12}, co-enzyme for the methionine synthase which mediates the transfer of a methyl group to homocysteine, converting it to methionine. We have previously shown that liver concentrations of methionine decrease after 80 min exposure to 50% nitrous oxide in rats [1]. The purpose of the present study was to see if i.p. administration of methionine could reverse the effects on DNA synthesis of exposure to nitrous oxide.

Male Sprague–Dawley rats were allocated randomly to four groups. Each group of six rats was exposed to either 50% oxygen–nitrogen or 50% oxygen–nitrous oxide, with or without methionine, for 3 h. Methionine 100 µmol was given i.p. at 0 and 1.5 h from start of exposure. (A single i.p. dose of methionine is known to increase plasma concentrations of methionine by a factor of × 10 for 3 h.) Placebo injections of saline were given to the control groups by the same method. DNA synthesis in marrow was assessed using the Deoxyuridine Suppression Test (DUST). Groups were compared using an unpaired two-tailed Wilcoxon test.

TABLE III. *DNA synthesis assessed by the deoxyuridine suppression test* (*DUST*) (*normal value* <10%)

Group	Exposure	Treatment	Mean (SD) DUST (%)	*P* (*v.* Group 1)
1	O_2/N_2	Saline	7.6 (2.3)	—
2	O_2/N_2	Methionine	8.1 (1.7)	ns
3	O_2/N_2O	Saline	16.7 (2.9)	<0.002
4	O_2/N_2O	Methionine	12.7 1.2	<0.005

Groups 3 and 4 were significantly different from each other ($P < 0.02$), but methionine did not completely restore the DUST to normal (table III). This suggests a more complex mechanism for nitrous oxide-mediated impairment of DNA synthesis than simple depletion of methionine. Methionine may be acting as a free-radical scavenger [2] or via inhibition of 5,10-methylene tetrahydrofolate reductase.

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PHARMACOLOGICAL RESPONSES IN VASCULAR SMOOTH MUSCLE DETERMINED BY ELASTANCE MEASUREMENT

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Existing strip preparations of arterial smooth muscle, whilst a sensitive means of displaying pharmacological responses, may suffer from poor drug access and wall hypoxia [1] and may suffer intimal damage during preparation, as may perfused arterial segments. We have therefore attempted to record pharmacological responses by direct measurement of vascular wall elastance.

We used continuously perfused segments of human uterine artery, dissected from the body of the uterus. Segments 1–2 cm long were cannulated at each end and mounted in a tissue bath containing physiological saline maintained at 37 (SD 0.5) °C and gassed with 5% carbon dioxide in oxygen. The physiological saline had the following ionic composition (mmol $litre^{-1}$): Na 134, K 4.5, Mg 1.2, Ca 2.5, Cl 119, HCO_3 22, SO_4 1.2, PO_4 1.2, plus the following organic substrates (mmol $litre^{-1}$): glucose 11, glucuronate 0.16, citrate 0.16, glutamate 0.06, pyruvate 0.09, ascorbate 0.05, aspartate 0.03. Using an LKB Varioperpex peristaltic pump, the tissue was perfused with the same solution, which has a pH of 7.35–7.45 after equilibration with the gas mixture.

In order to measure the vascular wall elastance, the flow was interrupted periodically using a computer controlled solenoid valve which obstructed the outflow from the arterial segment. The pressure within the segment was monitored continuously using Bell & Howell 4-327-I pressure transducers and a Lectromed Multitrace 4 recorder. The output from the transducers was monitored by a microcomputer which controlled the operation of the solenoid valves and the collection of data. During each occlusion, the pressure within the segment was measured at regular intervals and the rate of increase in pressure estimated by linear regression analysis. Since the volume delivered by the pump during the time of the occlusion could be calibrated, the vascular wall elastance was the gradient of the pressure increase (mm Hg μl^{-1}). This figure and its 95% confidence limits were displayed immediately as a plot on the computer screen.

In a refinement of this technique, the calculated elastance was returned to the chart recorder as an analogue signal. A further refinement allowed the computer to control directly the infusion pump motor, greatly increasing the working range of the technique.

We have used this technique to record pharmacological responses to noradrenaline in the human uterine artery, and are currently comparing the sensitivity of this method with that of conventional techniques.

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USE OF A RESPIRATORY MASS SPECTROMETER BY UNTRAINED PERSONNEL

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The Ohmeda 6000 multi-gas monitor is a mass spectrometer designed to be sufficiently small, robust and convenient in operation for routine anaesthetic monitoring. The purpose of this study was to establish the ease of its operation by untrained personnel with no prior instructions, either verbal or from an instruction manual.

Ten subjects took part in the study, none of whom had seen the instrument before the study or had any experience of operating a mass spectrometer. Each subject sat facing the Display/Control Unit with the instrument in the "Standby" mode. They were told that the instrument was designed to monitor respired gases and vapours and that their ability to operate the instrument was to be evaluated. No other introduction was given. The only information available to the subjects was provided on the electro-luminescent screen display.

Assessment was by means of a series of 14 tasks of varying complexity presented to the subject verbally. Each task introduced a single new operating procedure, for example "Set up the monitor for normal operation". Three indices of performance were used: the number of tasks successfully completed; the total number of buttons depressed in the course of completing the task; the time taken to complete the assessment. Results were compared with those achieved by an experienced user of this instrument.

Ten untrained operators attempted 14 tasks; one subject failed to complete two tasks and five failed to complete one task each—a success rate of 95%. Nine of the 10 completed the assessment with a button count less than twice that of the experienced operator, indicating a low error rate. The time taken to complete the assessment ranged between 1.6 and 4.8 (median 2.8) times that of the experienced operator. Repetition of the tasks revealed a rapid learning curve, more marked for time than for button count. Tasks causing particular problems were the autocalibration process and acknowledgement of alarm conditions by finding the "Acknow" key. The latter problem did not recur after the key was found.

The instrument could be used for clinical monitoring by medical and paramedical personnel with the minimum of difficulty in the majority of tasks. The instrument was robust and did not fail, nor was it damaged by unskilled handling.

SOURCES OF VARIABILITY WITH THE READ REBREATHING TECHNIQUE

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EFFECT OF RESPIRATORY ALKALOSIS ON OXYGEN CONSUMPTION UNDER GENERAL ANAESTHESIA

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Hyperventilation has been shown to increase oxygen consumption ($\dot{V}O_2$) in anaesthetized animals and awake human volun-

TABLE IV. *Mean (SD)* $\dot{V}O_2$ *for each 20-min interval for all three periods of ventilation.* *$P < 0.01$ *compared with times 20, 40, 60 in (A) and 40, 60 in (C)*

	(A) Normal ventilation			(B) Hyper-ventilation			(C) Normal ventilation		
Time (min):	20	40	60	20	40	60	20	40	60
$\dot{V}O_2$ (ml min^{-1})	206 (50)	203 (55)	201 (53)	213 (60)	216* (55)	225* (56)	213 (72)	206 (69)	204 (66)

teers [1, 2]. It is postulated that this increase in $\dot{V}O_2$ results from mitochondrial swelling secondary to an alkalosis-induced decrease in intracellular H^+ ion concentration. We determined whether hyperventilation to a Pa_{CO_2} approaching 2.7 kPa significantly altered $\dot{V}O_2$ in patients undergoing general anaesthesia with neuromuscular block.

Informed written consent for the study, which had been approved by the hospital review board, was obtained from each of eight patients (aged 20–40 yr) scheduled to undergo orthopaedic surgery of at least 4 h duration.

Anaesthesia was induced with methohexitone 1–2 mg kg^{-1}, sufentanil 1 µg kg^{-1} and vecuronium 0.1 mg kg^{-1}. The trachea was intubated and the lungs ventilated with 40% oxygen in air using a Servo 900B. Anaesthesia was maintained with infusions of methohexitone and sufentanil with increments of vecuronium to maintain neuromuscular block. Arterial pressure was monitored continuously via a radial arterial line and oesophageal temperature was maintained greater than 35.5 °C. $\dot{V}O_2$, end-tidal partial pressure of carbon dioxide (PE'_{CO_2}) and carbon dioxide excretion ($\dot{V}CO_2$) were measured using a metabolic gas monitor (MGM II, Utah Medical). $\dot{V}O_2$ and $\dot{V}CO_2$ were calculated and updated every 20 s. Following the start of surgery, respiratory gas exchange measurements began. $\dot{V}O_2$ was measured during consecutive 1-h periods of (A) normal ventilation (PE'_{CO_2} 4.3 kPa), (B) hyperventilation (PE'_{CO_2} 2–2.7 kPa) and (C) normal ventilation. Results were analysed using one-way analysis of variance and paired *t* tests.

From (A) to (B), Pa_{CO_2} decreased from 5.8 (SD 0.5) kPa to 2.9 (0.3) kPa ($P < 0.001$) and pH increased from 7.35 (0.04) to 7.53 (0.06) ($P < 0.001$). In (C) the values for Pa_{CO_2} and pH were similar to those for (A). $\dot{V}O_2$ increased significantly in the last 40 min (B) (table IV). This represented a 12% increase in $\dot{V}O_2$ when comparing the last 20 min of (B) with the last 20 min of (A).

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REGIONAL CEREBRAL BLOOD FLOW AND DOPPLER FLOW VELOCITY IN THE MIDDLE CEREBRAL ARTERY OF THE CAT

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Changes in cerebral blood flow (CBF) velocity profile occur in cerebrovascular disease, birth asphyxia and convulsions. Changes in derived indices are often used to infer changes in flow. Previous comparisons demonstrated correlation between some indices compared with hemispheric CBF estimated with microspheres or radioactive xenon, and no correlation with others [1]. We have compared regionally related estimates of regional cerebral blood flow (rCBF) and CBF velocity measured using Doppler ultrasound [2].

Simultaneous measurements of rCBF and CBF velocity were made in seven adult cats anaesthetized with 1% halothane and 70% nitrous oxide in oxygen. rCBF was measured by hydrogen clearance polarography using up to three platinum microelectrodes implanted through the dura exposed by a left parietal craniotomy into the sylvian gyrus. The middle cerebral artery, supplying this gyrus, was insonated with a 9.5 MHz continuous wave Doppler probe. Changes in rCBF were induced by adjustment of the concentration of carbon dioxide in the inspired gases. Control measurements were made at normocapnia (Pa_{CO_2} approximately 4.5 kPa) and the hypercapnia and hypocapnia (IL413) were induced in random order. Each animal was subjected to between five and 15 changes in Pa_{CO_2}. Before the animal was killed, oxygen was removed from the inspired gases to produce hypoxia, and reintroduced immediately before cardiac failure and the resulting post-hypoxic hyperaemia was recorded.

Regression equations for pooled results were $y = 54 + 6.6x$ for rCBF ($P = 0.02$), and $y = 21 + 2x$ for velocity ($P = 0.12$); thus for a doubling of Pa_{CO_2} there was a 40% change in rCBF and a 30% change in velocity (table V). Association between the measurements showed considerable scatter ($r = 0.25$, $P = 0.03$); comparison of absolute changes in rCBF and velocity showed a closer relationship ($r = 0.4$, $P = 0.03$).

Hypoxic insult ($n = 5$) caused a 157% increase from baseline in rCBF (range 37–263%) and an increase from baseline of 35% for velocity (range 0–70%).

Doppler estimation of CBF velocity was related to rCBF during changes induced by alteration of Pa_{CO_2}, but not hypoxia. Quantitative CBF cannot be calculated from rCBF, and the changes in velocity were consistently smaller than those

TABLE V. *Effect of carbon dioxide on regional cerebral blood flow (rCBF) and Doppler flow velocity (Velocity) in six cats.* n = *No. observations*

Cat No.	*n*	Pa_{CO_2} (kPa)	rCBF (ml/100 g min^{-1})	Velocity (cm s^{-1})
2	5	3.79–4.70	51–68	27–48
3	11	3.48–6.89	54–145	17–31
4	7	4.67–7.66	59–102	10–28
5	15	2.91–7.84	48–128	12–25
6	11	3.46–10.4	78–130	34–68
7	13	2.82–8.62	30–138	29–58

of rCBF. The errors were exaggerated with increasing values of rCBF.

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EFFECT OF ACUTE AFTERLOADING ON MYOCARDIUM WITH NORMAL AND CRITICALLY RESTRICTED BLOOD SUPPLY

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Cross-clamping of the aorta may cause ischaemic myocardial dysfunction in patients with ischaemic heart disease [1], and sensitive measures may detect dysfunction in normal myocardium. We investigated the effect of an acute occlusion of the descending aorta on the normal myocardium and myocardium with critically restricted blood supply, using sonomicrometry.

Instruments were placed in seven dogs, anaesthetized with halothane and artificially ventilated, to permit measurement of aortic and left ventricular pressure and left ventricular dimensions (sonomicrometry) in the subendocardium of the apex of the left ventricle (LV). A micrometer-controlled snare was placed around the left anterior descending coronary artery (LAD) and an occluding snare was placed around the descending aorta. Halothane was replaced by propofol (5-mg kg^{-1} bolus, 0.3-mg kg^{-1} min^{-1} infusion). Control recordings were made after 40 min. The descending aorta was occluded to increase arterial pressure by at least 40% and recordings repeated. The LAD was critically constricted and recordings of normal and afterloaded beats repeated. Systolic shortening (% of end-diastolic length: %SS), and postsystolic shortening (% of total shortening: %PSS) were measured. Data were analysed using two-way ANOVA, with Wilcoxon ranked paired tests and paired *t* tests.

Afterloading caused significantly greater reduction in %SS and increase in %PSS after critical constriction of the LAD (Table VI). During acute afterloading in the normal myocardium, systolic function was maintained, but some dysfunction developed during early diastole (PSS). However, in the myocardium with restricted blood supply, ischaemia developed, indicated by a decrease in %SS and a substantial increase in %PSS. As dysfunction may occur even in normal myocardium, care must be taken in intraoperative interpretation and treatment of wall motion abnormalities during aortic cross-clamping.

TABLE VI. *Mean (SD) heart rate (HR), systolic arterial pressure (SAP), and systolic (SS) and post systolic (PSS) shortening.* *$P < 0.05$ *afterloaded* v. *normal*; †$P < 0.05$ *afterloaded critical constriction* v. *afterloaded normal blood flow*

	Normal blood flow		Critical constriction	
	Normal	Afterloaded	Normal	Afterloaded
HR (beat min^{-1})	141 (28)	134 (33)	136 (27)	136 (27)
SAP (mm Hg)	96 (8)	145 (21)*	97 (8)	138 (12)*
SS (%)	27.5 (6.2)	27.5 (5)	27.3 (6.9)	19.7 (4.6)*†
PSS (%)	1.7 (3.2)	6.3 (4.9)*	2.2 (4.5)	22.9 (12.3)*†

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CONTINUOUS AMBULATORY ECG MONITORING FOR DETECTION OF PERIOPERATIVE ISCHAEMIA IN SURGICAL PATIENTS

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Ischaemic heart disease is present in up to 15% of patients presenting for non-cardiac surgery and is a major cause of postoperative morbidity and mortality. The incidence of postoperative myocardial infarction in a healthy population undergoing anaesthesia may be as low as 0.5%, but the incidence in patients with a previous myocardial infarction has been reported as up to 18% [1]. Attempts to correlate the preoperative condition of the patient with the postoperative outcome have lead to the development of Risk Factor Indexes. We are attempting to develop such an index for our local population in Sheffield.

As part of this study we have used continuous ambulatory ECG monitors for a period of up to 24 h before operation and for 48 h after operation in patients with known cardiovascular disease. The monitors used are Compas ambulatory units (Cardiac Care Units Inc.)—computerized ambulatory surveillance units which can be programmed to detect, record and signal ECG abnormalities in an ST segment or rhythm mode. They also produce a hardcopy summary of events recorded to a compatible printer system. The ECG algorithm depends on the simultaneous recording of three standard leads (aVf, V2, V5 in the ST segment configuration), with detection of any ST segment change lasting 30 s or more as well as any atypical beat morphology. In this configuration the computer printout gives a baseline ECG and numerical and graphic recordings of ST segment change, atypical beats, asystole and any patient marked events. As used in this mode on our patients, all alarms are disabled except for Tachycardia >170 beat min^{-1} and Bradycardia <31 beat min^{-1}.

Patient's preoperative history and examination, anaesthetic and type and duration of surgery were noted. All ST events and rate changes in ventricular ectopics were recorded and correlated with any clinically significant events such as drug therapy, oxygen therapy or cardiovascular instability.

Early findings of this study suggest that this is a useful tool for the early detection of ischaemia in the postoperative period and also suggest that hypertension, even when treated, may be an important prognostic factor in our patients. The monitor is about the size of a personal stereo, is quite robust and has proved acceptable to patients.

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NON-INVASIVE APPLICATION OF ELECTRO ACUPUNCTURE: A PERIOPERATIVE ANTI-EMETIC

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While manual or electro acupuncture (ACP) applied at the P6 point have a clearly demonstrable antiemetic effect in women premedicated with nalbuphine 10 mg, undergoing minor gynaecological operations under methohexitone–nitrous oxide–oxygen anaesthesia, these methods involve the correct placement of an ACP needle and are time-consuming. In an attempt to simplify the technique, we studied the use of an electrical conducting nickel plated cobalt stud placed over the P6 point and stimulated with 2.5–10 Hz d.c. for 5 min.

Three regimens were studied in random order and the findings compared with 10-Hz electro ACP also applied for 5 min (31 patients in each group) and with an untreated "control" group from an earlier study [1]. Patients were visited after operation by an observer who was unaware of the technique used. The occurrence of nausea alone or with vomiting was noted at the end of 1 and 6 h after operation.

Compared with the controls, all three forms of transcutaneous stimulation significantly reduced the frequency of sickness in the first 6 h after operation ($P < 0.001$–0.05) (table VII). Although none appeared to be as efficient as electro ACP, the difference was significant only in the bilateral 10-Hz group ($P < 0.05$). The maximum beneficial effect was noted in the first 1 h after operation, when the incidence of sickness in none of the groups was significantly different than after electro ACP. The best overall effect was obtained with a unilateral stud, stimulated at 5 Hz.

While the application of a current to a conducting stud applied over the P6 ACP point is not quite as effective an anti-emetic as that applied to an ACP needle, the advantages of simplicity and safety recommend its use.

TABLE VII. *Incidence of sickness during the first 6 h after operation. N = Nausea alone; V = vomiting (including retching) with or without nausea*

ACP	N	V	Nil
None	13	8	10
Needle			
Electro, 10 Hz	2	4	25
Studs			
Unilateral, 5 Hz	3	7	21
Bilateral, 2.5 Hz	8	4	19
Bilateral, 10 Hz	6	7	18

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CEREBROSPINAL FLUID AND PLASMA CONCENTRATIONS OF ATRACURIUM AND LAUDANOSINE IN MAN

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This study investigated transfer of laudanosine into the CSF when an atracurium infusion was used to provide neuromuscular block during neurosurgical procedures.

Following Ethics Committee approval, we studied nine patients (all with normal renal and hepatic function) undergoing clipping of intracranial aneurysms. Anaesthesia was with thiopentone 5 mg kg^{-1}, fentanyl 4 μg kg^{-1} and atracurium 0.6 mg kg^{-1} followed by an infusion of 0.5 mg kg^{-1} h^{-1}, maintained with 66% nitrous oxide in oxygen, supplemented with isoflurane. Ventilation was adjusted to keep $P_{E'CO_2}$ in the range 3.5–4.0 kPa. Core temperature was maintained between 36.5–37.5 °C. Neuromuscular block was monitored via the common peroneal nerve and the infusion of atracurium adjusted to keep the post-tetanic count less than 10. CSF samples were obtained via a lumbar spinal drain inserted immediately after tracheal intubation. Paired CSF and blood samples were taken at this time (0), and at 15, 30, 60 min and every 1 h thereafter until the end of surgery. All samples were immediately centrifuged and 0.2 ml of supernatant decanted into 0.8 ml of cooled sulphuric acid (pH 1.5) and frozen at −20 °C until required for assay by HPLC [1].

The mean time for infusion of atracurium was 165.7 min (range 111–251 min); mean infusion rate was 0.5 mg kg^{-1} h^{-1} (range 0.3–1.0 mg kg^{-1} h^{-1}) and post-tetanic count was 3–9. There were no significant changes in plasma concentrations of atracurium during the infusion period. Plasma concentrations of laudanosine increased with time; CSF concentration of laudanosine also increased, but at a greater rate, during the same period. This was reflected in a progressive increase in CSF:plasma ratio (table VIII).

Laudanosine is known to induce seizures in anaesthetized dogs when the plasma concentration exceeds 17 μg ml^{-1} [2]. We have demonstrated that the transfer of laudanosine into the CSF during the first 2 h of an infusion of atracurium is less rapid in man than after an i.v. bolus in dogs [3].

TABLE VIII. *Mean (SEM) concentrations of atracurium and laudanosine during the study.* $P < 0.05$: ** compared with 0 min; † compared with previous value (Wilcoxon test)*

	Time (min)				
	0	15	30	60	120
Plasma atracurium	3.70	3.41	3.13	3.44	3.15
($\mu g\ ml^{-1}$)	(0.30)	(0.47)	(0.51)	(0.36)	(0.36)
Plasma laudanosine	1023	1020	1258	1290	1449*
($ng\ ml^{-1}$)	(305)	(208)	(208)	(170)	(261)
CSF laudanosine	0	20	34	120	203
($ng\ ml^{-1}$)		(10)	(21)	(36)	(60)
CFS: plasma ratio	0	0.02	0.03†	0.09†	0.14†
n	7	9	9	9	8

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MOVEMENT OF THE TONGUE ON INDUCTION OF ANAESTHESIA

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Airway obstruction in anaesthesia is often attributed to "falling back" of the tongue [1]. We used ultrasound to measure tongue movement during induction of anaesthesia [2]. With local Ethics Committee approval and informed consent, we studied women about to undergo minor gynaecological procedures.

The patient relaxed on a trolley with her head in a natural position on a single pillow. A 3.5-MHz mechanical sector scanning probe (Siemens sonoline SX) was placed below the chin to give an ultrasound image of a sagittal midline section of the tongue, and clamped in the position that gave the best image. As anaesthesia was induced with either thiopentone or propofol, a video recording was made until at least 1 min after loss of consciousness.

Photographs, chosen to show a good tongue image, were taken from the replayed video recording: two from the period before and two after induction of anaesthesia. In some subjects in whom obstruction occurred, movements of the posterior tongue in time with ventilatory movements were noted: in these cases, photographs were taken during expiration. Pairs of photographs were coded in random sequence.

The tongue outline was obtained as the best fit from the pair of pictures obtained in each state. The outlines obtained before and after induction of anaesthesia were compared by measuring along the radius of the sector, to anterior, middle and posterior points of the tongue surface. Distances were converted into actual movement. Generally, the posterior tongue was more difficult to visualize, because of the shadow cast by the hyoid. Satisfactory data were obtained in 11 patients. Movements observed were small; there was no consistent direction of movement, relationship between movement and the presence of clinically apparent airway obstruction, or difference between the two induction agents. The probability of any movement of more than 8 mm was between 0 and 28% (95% confidence limits, binomial distribution).

We conclude that tongue movement on induction of anaesthesia is small and inconsistent.

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COMPLICATIONS ASSOCIATED WITH INHALATION ANAESTHESIA

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Using the Nominal Group Method [1], 16 complications of inhalation anaesthesia were identified. Between December 1987 and May 1988, according to printed criteria on a special card, all anaesthetists in south east Scotland entered the occurrence of complications for each patient to whom halothane, enflurane or isoflurane was given on a free choice basis. Other information collected included age, body size of the patient, type of induction of anaesthesia, administration of suxamethonium, tracheal intubation and IPPV.

There were 16995 patients from 17 general and specialist hospitals. Compliance in the study was estimated at about 75% of available patients. The relationship between complications and available factors was examined for each factor separately, using chi-squared tests and then multiple logistic regression.

There was an association between choice of inhalation agent and tachycardia, bradycardia, cardiac arrhythmias and arterial hypotension, but not observed ECG changes suggestive of myocardial ischaemia (although age was a significant factor in such ischaemic changes). Inhalation agent also appeared to influence the incidence of breath-holding, laryngeal spasm, respiratory depression, difficulty in controlling the depth of anaesthesia and delayed recovery from anaesthesia.

Age was a factor in cardiovascular complications; weight in the incidence of breath-holding, troublesome secretions and difficulty in controlling depth of anaesthesia. The seniority of the anaesthetist was a factor in tachycardia, hypotension and laryngeal spasm.

An unexpected finding was differences between hospitals in levels of reporting of some complications.

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ROPIVACAINE: A PRELIMINARY CLINICAL TRIAL

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Ropivacaine is a new amino-acyl-amide local anaesthetic agent. Animal and human volunteer studies have indicated that it is less toxic to the cardiovascular system than bupivacaine, but that it has a similar potency. We report a preliminary, open, dose-finding study of ropivacaine in extradural block in man. Twenty patients (aged 51–74 yr) who were to undergo transurethral resection of the prostate gland under extradural block gave informed consent for the study, which was approved by the local Ethics Committee.

The patients were premedicated with diazepam 10 mg, given about 1 h before the block. No additional medication was given for surgery unless the patient complained of pain. Each patient had a 16-gauge end-hole extradural catheter inserted at the L2/3 or L3/4 space. They were placed supine and 2% lignocaine 3 ml with adrenaline 1:200000 was injected. Five minutes later, 0.5% bupivacaine 20 ml or 0.5%, 0.75% or 1.0% ropivacaine was injected incrementally over 3 min. The segmental level of analgesia to pinprick and the degree of motor block (Bromage scale 0–3) were assessed every 5 min for 30 min and then every 15–30 min until the block had regressed completely. Heart rate and arterial pressure were measured at the same intervals.

The median maximum block height was greater after 0.75% and 1.0% ropivacaine than after bupivacaine or 0.5% ropivacaine (table IX). The median time to maximum block height was longest with bupivacaine and decreased with increasing concentration of ropivacaine. Median duration of block was similar in all groups, and tended to increase with increasing concentration of ropivacaine.

All patients who received 1% ropivacaine had completely adequate analgesia. Supplementary analgesics were required in two patients in each of the other groups. The results indicate that ropivacaine is an effective agent for extradural block in man and merits further investigation. Parallel studies performed at Charing Cross Hospital (Drs A. Rubin and B. Arrigoni) and at St Thomas' Hospital (Drs C. Pither and E. Whitehead) have produced similar conclusions.

TABLE IX. *Extradural block (median) induced by 0.5%, 0.75% or 1.0% ropivacaine and 0.5% bupivacaine*

	Ropivacaine (%)			Bupiv. (%)
	0.5	0.75	1.0	0.5
Maximum dermatome (range)	T4–T7	C5–T6	C2–T5	T4–T10
Time to max. height (min)	25	20	15	30
Duration at T12 (min)	255	360	315	240
Total duration (min)	330	360	390	300

EFFECTS OF FLUORINATED CONVULSANTS AND ANAESTHETICS ON THE POTASSIUM CONDUCTANCE OF THE SQUID AXON

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Most inhalation anaesthetics are fluorinated hydrocarbons or ethers, but many similar molecules are convulsants. The origins of these differences in biological activity are poorly understood. We have used the squid axon as a model system to study the membrane actions of the anaesthetics enflurane and isoflurane, and the convulsants fluorothyl (indoklon, $CF_3CH_2OCH_2CF_3$) and trichlorofluoromethane (CCl_3F).

Using established methods [1], experiments were performed on axons dissected from freshly-killed squid. We examined the effects of test substances on: the resting potential (V_R); the threshold 100-μs current (I_0) required to stimulate an action potential; the conductance of the axon membrane (g_K) in high-potassium solution containing tetrodotoxin and 3,4-diaminopyridine to block the sodium and potassium channels, respectively; and the maximum voltage-clamp inward sodium current (I_{Na}). g_K was an estimate of the voltage-independent K^+ conductance of the membrane [1].

All test substances at clinical concentrations caused depolarization of V_R (table X). The significant reductions in I_0 show that all four substances caused hyperexcitability in this model at these concentrations, apparently as a result of marked inhibition of a voltage-independent K^+ conductance, estimated as g_K. The changes in V_R and I_c can be accounted for quantitatively by changes in g_K of the magnitude shown here [2].

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†Professor D. A. Haydon died in November 1988.

TABLE X. *Mean shifts in* V_R *and mean changes in other variables* (n = *2–4*)

Substance	Concn (mmol litre^{-1})	V_R shift (mV)	Mean changes (%)		
			I_o	g_k	I_{Na}
Fluorothyl	0.5	+2.2	−29	−76	−3
CCl_3F	0.5	+2.4	−25	−64	−2
Enflurane	0.8	+3.1	−41	−79	−13
Isoflurane	0.4	+2.3	−28	−40	−7

The sodium current (I_{Na}) was relatively unaffected by the concentrations cited in table X. However, at 5 to 10 times greater concentrations, enflurane and isoflurane inhibited I_{Na} by approximately 50%, while fluorothyl and CCl_3F still did not suppress I_{Na}.

These results suggest that the fluorinated convulsants act by inhibition of a voltage-independent K^+ conductance. The balance between anaesthetic and convulsant action may relate to differential effects on this potassium conductance and on the voltage-dependent conductances. In this model, enflurane and isoflurane are partial convulsants, and it is of interest that convulsant-like EEG activity occurs during anaesthesia with enflurane [3].

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EFFECT OF PREOPERATIVE WATER, FAMOTIDINE OR RANITIDINE ON GASTRIC VOLUME AND pH

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Preoperative oral fluids do not increase residual gastric volume (RGV) at induction of anaesthesia; oral ranitidine 150 mg with the oral fluid decreases both volume and acidity [1]. Similar findings have been reported with 100 ml of water given before operation [2]. We studied famotidine, a new histamine (H_2) receptor antagonist which has not been evaluated in the reduction of acid aspiration risk factors.

After Ethics Committee approval and informed consent, 180 healthy fasting adults receiving general anaesthesia for elective minor surgery were allocated randomly and double-blind to one of six pretreatment regimens:

Group 1 (P10) = placebo + water 10 ml
Group 2 (P150) = placebo + water 150 ml
Group 3 (R10) = ranitidine 150 mg + water 10 ml
Group 4 (R150) = ranitidine 150 mg + water 150 ml
Group 5 (F10) = famotidine 20 mg + water 10 ml
Group 6 (F150) = famotidine 20 mg + water 150 ml

TABLE XI. *Effects of placebo, ranitidine and famotidine on residual gastric volume and pH.* *P < *0.001 compared with groups 1, 2 or (1+2)*

Group	*n*	RGV (ml)		pH	
		Mean	Range	Median	Range
1 (P10)	24	25	3–100	1.6	1.1–3.2
2 (P150)	27	24	5–58	1.6	1.3–3.2
3 (R10)	26	11*	2–29	6.2*	2.0–8.5
4 (R150)	25	13*	1–36	6.3*	1.3–6.9
5 (F10)	24	12*	2–52	6.1*	1.4–7.0
6 (F150)	21	10*	2–30	6.3*	1.5–7.9
Placebo (1+2)	51	24	3–100	1.6	1.1–3.2
H_2 Antag. (3+4+5+6)	96	11*	1–52	6.2*	1.3–8.5

Pretreatment was 2 h before anticipated time of surgery; no other premedication was given. Following induction of anaesthesia, gastric contents were aspirated and their volume and pH measured. Analysis of variance and Mann–Whitney *U* test were used for statistical evaluation and $P < 0.05$ was considered significant. Patients in whom no gastric sample was obtained were excluded from statistical analysis.

The groups were comparable for mean age, weight, fasting interval (mean 12 h) and pretreatment to sampling interval (mean 135 min). Groups 1 and 2 were not different as regards to pH or RGV (table XI). Similarly, no significant differences were found between the various H_2-antagonist pretreated groups regardless of concomitant water ingestion (groups 3–6). The H_2-antagonist pretreated groups all had significantly reduced RGV and increases in pH when compared with placebo groups (1, 2 or 1+2) ($P < 0.001$).

We confirm that controlled administration of water 150 ml 2 h before induction may not be harmful to patients. The use of famotidine or ranitidine decreased the volume and acidity of the gastric environment when compared with placebo.

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GASTRO-OESOPHAGEAL REFLUX IN PREGNANCY AT TERM AND AFTER DELIVERY

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Pregnant women at term who require a general anaesthetic must be protected against the risks of regurgitation and possible aspiration pneumonitis, which are increased by gastro-oesophageal reflux in these women.

In this study, for which Ethics Committee approval was obtained, an antimony pH electrode [1] was placed in the oesophagus to investigate the incidence of spontaneous and provoked reflux in conscious pregnant women beyond 36 weeks of gestation and at about 36 h after delivery. Informed consent was given by 28 of 85 patients who were asked (about 35 %); 25 were studied both before and after delivery. All but three had symptoms of reflux at term; none had symptoms before pregnancy. Patients were starved for 4 h and did not smoke for 2 h before the study.

The electrode was introduced through the anaesthetized nose and swallowed with 200 ml of tap water. Gastric pH was measured before the electrode was withdrawn to the gastro-oesophageal junction, identified by a sudden increase in pH. The final position of the electrode was 5 cm above that point. The electrode is only 2 mm in diameter and was well tolerated by all the patients. A reflux episode was defined as a decrease in lower oesophageal pH from the normal value of about 6 to less than 4.

The patients were studied in four positions: supine with 15° of left tilt, left lateral, right lateral, and lithotomy with 15° of left tilt. If there was no spontaneous reflux in 5 min the patient carried out a sequence of manoeuvres designed to provoke reflux: they were asked to cough, to strain (Valsalva), then to sniff with the nose pinched (Mueller). If there was a reflux the oesophageal pH was allowed to return to normal before the patient assumed the next position. This test of reflux is similar to the Standard Acid Reflux Test [2]. The pH data were stored digitally and analysed later by computer program (Digitrapper and Oesophogram, Synectics Medical).

At term 17 of 25 patients had reflux and between them a total of 29 reflux episodes were seen: 16 spontaneous and 13 provoked. After delivery, five of 25 patients each had one episode of reflux. The decrease from 17 to 5 is significant ($P < 0.05$; chi squared with Yates's correction).

Some refluxes (three of 29 at term and three of five after delivery) lasted less than 12 s. Twenty-six of Skinner's 91 normal subjects [2] showed similar short refluxes, so the high incidence of reflux found at term is probably approaching normal by the second day after delivery. It is not yet possible to make a clear statement about when specific precautions against regurgitation and acid aspiration can safely be discontinued after delivery.

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HAEMODYNAMIC EFFECTS OF DOXACURIUM, PANCURONIUM AND VECURONIUM IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING

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Doxacurium (BW A938U) is a new long-acting non-depolarizing neuromuscular blocking agent which has minimal cardiovascular effects and a duration of action similar to that of pancuronium [1]. This study compared the haemodynamic effects of single equipotent doses of doxacurium (D), pancuronium (P) and vecuronium (V) in patients during anaesthesia for coronary artery bypass grafting.

After Ethics Committee approval and informed written consent, 27 patients were allocated randomly to three equal groups. Premedication was with oral lorazepam 2–4 mg and i.m. papaveretum 15–20 mg with hyoscine 0.3–0.4 mg. Radial artery and peripheral venous cannulae and a pulmonary artery thermodilution catheter were inserted under local anaesthesia. Atropine 0.4 mg was given i.v. 20 min before induction of anaesthesia with fentanyl 500 µg, diazemuls 5–10 mg and thiopentone 50–500 mg. After administration of suxamethonium 1 mg kg^{-1} and topical lignocaine, the trachea was intubated and the lungs ventilated to normocapnia with 50 % nitrous oxide in oxygen. A 1.5 × ED_{95} dose of

TABLE XII. *Mean (SEM) MAP, HR, CI, PAP, PCWP and CVP before (control) and at 1, 5 and 10 min after administration of doxacurium (D), pancuronium (P) or vecuronium (V)*

		Control	+1 min	+5 min	+10 min
MAP	D	73.9 (2.3)	72.8 (1.8)	75.4 (1.9)	74.6 (2.0)
(mm Hg)	P	75.0 (2.2)	80.1 (1.4)	80.9 (1.8)	80.9 (1.6)
	V	81.7 (6.1)	79.4 (7.2)	80.4 (7.5)	80.0 (7.5)
HR	D	59.4 (2.8)	58.7 (2.8)	58.3 (3.0)	57.9 (3.1)
(beat min^{-1})	P	56.7 (2.4)	62.4 (2.3)	63.7 (2.4)	65.0 (1.7)
	V	59.9 (2.7)	56.1 (1.6)	54.1 (1.6)	53.3 (1.6)
CI	D	2.3 (0.1)	2.4 (0.1)	2.5 (0.2)	2.4 (0.2)
(litre min^{-1} m^{-2})	P	2.3 (0.2)	2.7 (0.2)	2.7 (0.1)	2.6 (0.2)
	V	2.3 (0.1)	2.4 (0.1)	2.3 (0.1)	2.3 (0.1)
PAP	D	19.9 (2.0)	19.1 (1.6)	18.2 (1.6)	17.9 (1.6)
(mm Hg)	P	17.2 (1.2)	16.0 (1.6)	16.2 (1.7)	15.4 (1.8)
	V	19.1 (1.4)	18.1 (1.5)	17.2 (1.5)	17.3 (1.3)
PCWP	D	11.8 (1.6)	10.9 (1.5)	9.7 (0.7)	9.7 (0.8)
(mm Hg)	P	8.8 (0.9)	8.4 (1.4)	7.7 (1.3)	7.5 (1.1)
	V	11.2 (1.2)	9.3 (1.2)	9.7 (1.3)	9.6 (1.2)
CVP	D	9.3 (1.8)	7.4 (1.0)	6.5 (0.8)	6.5 (0.7)
(mm Hg)	P	6.5 (0.9)	4.5 (0.8)	4.3 (1.0)	4.1 (1.0)
	V	7.7 (0.9)	5.5 (1.3)	4.5 (1.5)	4.8 (1.6)

doxacurium (0.037 mg kg^{-1}), pancuronium (0.09 mg kg^{-1}), or vecuronium (0.075 mg kg^{-1}) was administered when measurements were stable and at least 20 min after intubation.

Continuous recordings were made of AP, pulmonary artery pressure (PAP) and ECG. Recordings of pulmonary capillary wedge pressure (PCWP) and central venous pressure (CVP) and measurements of cardiac output were made before and 1, 5 and 10 min after administration of the non-depolarizing neuromuscular blocker. Changes within the groups over time were tested using repeated measures ANOVA ($P < 0.05$ significant). There were no significant changes in mean arterial pressure (MAP), heart rate (HR) and cardiac index (CI) in patients given doxacurium. MAP, HR and CI all altered significantly in patients receiving pancuronium, and HR decreased significantly in patients who had vecuronium (table XII).

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NEUROMUSCULAR EFFECTS OF PIPECURONIUM BROMIDE

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The non-depolarizing neuromuscular blocker, pipecuronium bromide, has an ED$_{95}$ of approximately 45 µg kg^{-1} [1]. We have determined the onset and duration of its neuromuscular blocking action.

With their informed consent and approval from the local Ethics Committee, adult ASA grade I or II patients scheduled to undergo elective surgery were included in the study. Following premedication with oral diazepam, anaesthesia was induced with fentanyl 2–3 µg kg^{-1} and thiopentone 4–5 mg kg^{-1} and maintained with 70% nitrous oxide in oxygen and further increments of fentanyl or 0.5% halothane.

Heart rate, indirect arterial pressure, end-tidal carbon dioxide concentration and oxygen saturation were monitored throughout and ventilation adjusted to maintain normocapnia. Neuromuscular block was monitored by the stimulation of the ulnar nerve at the wrist using either single twitch (ST) at 0.1 Hz or train-of-four (TOF) modes of stimulation at 2 Hz every 10 s and recording the force of contraction of the adductor pollicis muscle. Pipecuronium 45 µg kg^{-1} was administered after stabilization of the control twitch height. The maximal depression of ST or T1 in the TOF and the time taken to attain it were recorded in every case, as was the time to recovery to 25% of control or more, where possible.

Results (table XIII) were subjected to analysis of variance and *t* tests. The degree of maximal block obtained varied between 96 and 99%. The time taken to attain the maximal block varied between 3.4 and 5.8 min. Onset times were significantly shorter with TOF stimulation, but there was no difference between the fentanyl and halothane groups. With ST stimulation, however, maximum block occurred significantly faster in the halothane group. The time to 25% recovery of ST or T1 varied between 41 and 54 min. Halothane anaesthesia prolonged the effect within each mode of stimulation, but the difference was significant in the ST groups only. Spontaneous recovery of ST or T1 to 75% was possible in only 28 patients and showed the recovery index (25–75% recovery) to be approximately 29 min.

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TABLE XIII. *Onset and duration of action (mean (SD)).* $P < 0.05$: **compared with other groups; †compared with ST and TOF fentanyl groups.* n = *No. patients*

	ST		TOF	
	Fentanyl ($n = 19$)	Halothane ($n = 18$)	Fentanyl ($n = 18$)	Halothane ($n = 18$)
Maximum block (%)	96 (3.8)*	99 (2.3)	98 (2.1)	99 (1.5)
Time to maximum block (min)	5.8 (1.5)*	4.3 (1.1)*	3.4 (0.5)	3.6 (0.5)
Time to 25% recovery (min)	41 (12.9)	54 (15.5)†	42 (9.8)	47 (12.8)
Time to 50% recovery (min)	53 (11.9) ($n = 5$)	60 (13.0) ($n = 8$)	48 (9.7) ($n = 13$)	62 (14.6) ($n = 13$)
Time to 75% recovery (min)	69 (11.3) ($n = 5$)	76 (17.3) ($n = 8$)	58 (5.1) ($n = 5$)	73 (19.2) ($n = 10$)

CHARACTERISTICS OF ATRACURIUM BLOCK IN THE GASTROCNEMIUS MUSCLE

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The muscles of the leg provide a convenient site for monitoring muscle relaxation during surgery, but little is known about their relative sensitivity to neuromuscular blocking drugs compared with the "yard-stick" adductor pollicis muscle. The present study compared these muscles during onset and offset of atracurium block, using paired measurements.

TABLE XIV. *Characteristics of block in the two muscles (means, range)*

	Adductor pollicis	Gastrocnemius
Maximum block (%)	86.9 (78.0–96.0)	91.6 (73.0–98.0)
Recovery Index (25%–75%) (min)	12.9 (11.0–14.4)	11.8 (9.5–14.9)
TOF ratio		
At max. block	0.17 (0.1–0.24)	0.17 (0.08–0.3)
At 25% recovery	0.2 (0.17–0.24)	0.21 (0.06–0.40)
At 75% recovery	0.35 (0.28–0.43)	0.50 (0.27–0.7)

Five adults undergoing elective surgery were investigated, with Ethics Committee approval. Anaesthesia comprised thiopentone 5–7 mg kg^{-1}, fentanyl 2–3 μg kg^{-1} and 67% nitrous oxide in oxygen. Ventilation was adjusted to maintain normocapnia and 1% enflurane was introduced after tracheal intubation. The ulnar and posterior tibial nerves were stimulated simultaneously with supramaximal pulses of 0.2 ms duration at 20-s intervals (surface electrodes). Trains-of-four stimuli were interposed at maximum block, 25% recovery and 75% recovery in each muscle. The compound action potentials of the adductor pollicis and the gastrocnemius were displayed on an oscilloscope and recorded using a two-channel electromyograph (Dantec 2000M). Peak-to-peak amplitude was measured. Following induction of anaesthesia and stabilization of the EMG, atracurium 0.23 mg kg^{-1} (ED$_{95}$) was given i.v. EMG recording continued until 75% recovery of the first response of the train-of-four. Student's paired *t* test was used to analyse the results.

The pattern of block of the adductor pollicis was reflected very closely by the gastrocnemius ($P > 0.05$, all indices) (table XIV). This was unexpected, in view of the differences in the proportion of slow fibres (gastrocnemius 50%, adductor pollicis 80%) [1], which may be more susceptible to neuromuscular block in man [2].

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MONITORING OF VECURONIUM-INDUCED NEUROMUSCULAR BLOCK: COMPARISON OF MECHANOMYOGRAPHY AND INTEGRATED ELECTROMYOGRAPHY

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The Datex Relaxograph, which records evoked integrated electromyographic responses (IEMG), has been introduced as a simple monitor of neuromuscular block and as a possible replacement for mechanomyography (MMG). However, a recent study has shown significant differences between IEMG and MMG during measurement of suxamethonium block [1]. In this study we have compared the IEMG and MMG monitoring during neuromuscular block with vecuronium.

Twenty ASA I or II patients (16–65 yr) were studied with their informed consent and Ethics Committee approval. After premedication with diazepam and induction of anaesthesia with thiopentone 5–6 mg kg^{-1}, patients' lungs were ventilated to normocapnia with 70% nitrous oxide in oxygen and 0.45% (end-tidal) halothane. The IEMG responses of the hypothenar muscles of one hand and the mechanical twitch responses of the adductor pollicis of the other to train-of-four (TOF) stimulation of the ulnar nerve at 2 Hz every 10 s were recorded simultaneously. Groups of 10 patients each were randomly allocated to receive vecuronium 40 or 80 μg kg^{-1}. IEMG and MMG responses were recorded during onset and recovery of block. Results were compared using paired *t* tests.

IEMG showed significantly less depression of the first twitch in the TOF (T1) with the lower dose of vecuronium. Time to onset of maximum block was significantly longer with IEMG monitoring with both doses of vecuronium (table XV).

The time to 25% recovery of T1 was similar with both methods of monitoring following both doses of vecuronium, as was the time to the reappearance of T4 with the 80-μg kg^{-1} dose. The times to recovery of T1 to 25, 50, 75 and 100% and the recovery index after the 40-μg kg^{-1} dose (where full spontaneous recovery was allowed) were not significantly different for IEMG and MMG. However, one and six patients failed to achieve 75 and 100% recovery, respectively,

TABLE XV. *Onset and recovery of block with vecuronium (mean (SD)).* *P < *0.05 between MMG and IEMG.* n = *10 except where shown*

	MMG		IEMG
40 μg kg^{-1}			
Max. block (%)	97.0 (3.59)	*	93.1 (5.07)
Onset time (s)	220.9 (40.39)	*	259.3 (50.41)
Recovery (min)			
T1 = 25%	13.8 (4.19)		13.8 (6.03)
T1 = 50%	18.8 (5.28)		18.0 (6.44)
T1 = 75%	23.2 (6.60)		21.7 (8.41) ($n = 9$)
T1 = 100%	29.8 (9.08)		23.1 (9.02) ($n = 4$)
Recovery index (T1 25–75%) (min)	9.4 (3.12)		8.2 (2.70) ($n = 9$)
TOF at T1 = 25%	0.14 (0.09) ($n = 5$)		0.16 (0.10) ($n = 7$)
TOF at T1 = 50%	0.25 (0.08) ($n = 9$)	*	0.15 (0.07)
TOF at T1 = 75%	0.42 (0.10)		0.26 (0.12) ($n = 9$)
TOF at T1 = 100%	0.66 (0.08)		0.41 (0.23) ($n = 4$)
80 μg kg^{-1}			
Max. block (%)	100		100
Onset time (s)	141.4 (28.20)	*	179.6 (58.94)
Recovery (min)			
T1 = 25%	31.6 (5.65)		30.3 (4.27)
T4	32.9 (5.65)		31.8 (5.73)

with IEMG despite full recovery with MMG. TOF ratios during recovery were lower with the IEMG, except at T1 25%.

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RELATIONSHIP BETWEEN AIRWAY DEADSPACE AND LUNG VOLUME IN ANAESTHETIZED PATIENTS: EFFECTS OF STERNOTOMY

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A study of the relationship between the airway deadspace (V_D^{aw}), lung volume and tidal volume (V_T) in adults found that V_D^{aw} correlated positively with lung volume and with tidal volume, most markedly at small tidal volumes [1]. It was concluded that most of the distensibility of the airway deadspace lay in the small airways, and that the small airways were almost as distensible as the alveoli.

We have reviewed published and unpublished studies in which V_D^{aw} and functional residual capacity (FRC) were measured before and after sternotomy, a procedure known to increase lung volume. V_D^{aw} was measured by carbon dioxide single breath test, and FRC by SF_6 washout.

After insertion of a sternal retractor, mean FRC increased from 1.7 litre to 2.6 litre (mean increase 55 (20)%, $n = 8$) [2] in adults and mean V_D^{aw} increased from 86 to 115 ml (34 (15)%, $n = 22$) [3]. In children undergoing sternotomy, the increases were 21 (13)% for FRC ($n = 10$, median age 11 months) and 16 (13)% for V_D^{aw} ($n = 20$, median age 15 months). In children, but not in adults, the percent increase in V_D^{aw} caused by sternotomy was correlated to age ($r = 0.48$). In those children in whom tidal volume was slightly reduced after sternotomy, there was frequently no increase in V_D^{aw}.

The airway deadspace (V_D^{aw}) extends from the airway opening to the interface formed in the respiratory bronchioles between inspired gas and alveolar gas. Its magnitude is affected both by breathing pattern (e.g. an end-inspiratory pause reduces it) and by changes in airway calibre. Thus it varies considerably with changes in FRC. Adults show a greater ($P < 0.01$) increase in lung volume than children after sternotomy, possibly because the adult thorax is rigid; children have a soft rib cage, the expansion of which is limited by the negative intrapleural pressure.

The percent increase in V_D^{aw} was approximately the same as that in FRC in children, but only about half as much in adults. A possible explanation for this difference lies in the lack of rigidity in the child's bronchial tree. The first 11 generations of the tree are cartilaginous and in adults, this restricts their dilatation in response to an increase in lung volume; in children, in whom cartilage is soft, even these generations are likely to vary in calibre in response to changes in lung volume.

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PREOPERATIVE ARTERIAL PRESSURE MEASUREMENTS: RELATIONSHIP TO RESTING VALUES

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Kaplan has noted a transient increase in arterial pressure (AP) caused by manual measurement [1]. All AP measurements in conscious patients could be affected by this stress response, including preoperative and anaesthetic room measurements. We determine resting (plateau) arterial pressure and examined its relationship to AP on admission to the ward, and to AP in the anaesthetic room before induction of anaesthesia.

Informed consent was obtained from 30 normotensive patients scheduled to undergo elective surgery. After a routine preoperative visit, the patient relaxed supine, undisturbed and behind screens. A Dinamap, out of sight of the patient, recorded arterial pressure at 1-min intervals for 15 min.

Premedication was with temazepam 20 mg, 2 h before induction of anaesthesia. In the anaesthetic room, the same Dinamap was used to read AP from the same arm at 40-s intervals.

On the ward, in 29 of 30 patients, the initial AP decreased to a plateau, which we had defined as the mean of the last five readings. The initial systolic AP was significantly different (paired *t*) from the plateau systolic ($P < 0.001$) (table XVI). Five patients were initially "hypertensive" (AP > 140/90 mm Hg), but their plateau pressures were normal. The correlation coefficients between the initial ward systolic pressures and the initial pressures in the anaesthetic room were greater than 0.69 ($P < 0.001$). The anaesthetic room systolic AP was not significantly different from the initial pressure on the ward, but was significantly different from the plateau pressure ($P < 0.001$). Eight patients were "hypertensive" before induction of anaesthesia, but normal on the ward. Measurements by nurses were poor indicators of Dinamap results.

TABLE XVI. *Mean arterial pressures (SD)*

	Initial	Plateau	Anaesthetic room
Systolic	135.9	123.77	133.77
(mm Hg)	(17.37)	(12.94)	(15.82)
Diastolic	77.63	70.13	79.76
(mm Hg)	(12.09)	(10.1)	(15.24)

In this study, AP on the ward and in the anaesthetic room differed significantly from resting AP. The transient stress response termed white coat hypertension by Kaplan should be considered when evaluating the cardiovascular system before anaesthesia. It could affect decisions to postpone surgery and anaesthesia pending investigation of hypertension.

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HAEMODYNAMIC EFFECTS OF AN IMPLANTABLE LEFT VENTRICULAR ASSIST DEVICE (LVAD) IN THE CALF

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Despite maximal medical and conventional cardiac surgical therapy, there remains a large number of patients who suffer and ultimately die from heart failure. Heart transplantation is limited by the shortage of donor organs and stringent acceptance criteria. Therefore, mechanical circulatory support devices are being developed. We report our initial haemodynamic findings with an implantable pneumatic, pusher plate LVAD (Thermedics Inc., Woburn, Ma.) in the calf.

The LVAD was inserted into six calves (mean age 14.5 weeks, mean weight 77.8 kg) sedated with xylazine 0.4 mg kg^{-1} i.v. or i.m. and with a left jugular catheter inserted. Thiopentone 4–7 mg kg^{-1} was then given before tracheal intubation and anaesthesia was continued using isoflurane, nitrous oxide and oxygen. Vecuronium 1 mg kg^{-1} was used to obtain neuromuscular block. A thermodilution pulmonary artery catheter (Amercian Edwards 93A) was inserted via the left jugular vein, and a femoral artery catheter inserted to monitor systemic arterial pressure (AP) and allow for arterial blood sampling. A urinary catheter and orogastric tube were placed also. At this time measurements were made of AP, central venous pressure (CVP), heart rate (HR), pulmonary capillary wedge pressure (PCWP), pulmonary artery pressure (PAP) and cardiac output (CO) (pulmonary artery catheter) (Gould SP1435, Bently 800, Kontron 7210, Devices M19).

The LVAD was placed beneath the left hemidiaphragm. The inlet conduit was placed through the apex of the left ventricle and the outlet conduit was anastomosed to the descending thoracic aorta. A pneumatic power and electronic monitoring line passed through the lateral abdominal wall to the control module. After removal of air, the device was activated and set on a fixed rate of 80 beat min^{-1}. An epicardial echocardiogram was performed in three of the animals at this time. Following wound closure, the haemodynamic measurements were repeated.

Six animals have been studied, their survival ranging between 12 h and 3 months after implantation. There was no significant difference (*t* test) between haemodyamic variables measured before and after insertion of the device (table XVII).

Following activation of the device, 75 % of the total cardiac output (as measured by the thermodilution catheter) is actually being generated by the LVAD (as displayed on the control module). This is reinforced by the echocardiographic findings of reduced left ventricular cavity size and reduced left ventricular outflow tract flow measured by Doppler. These findings suggest that this device is capable of supporting an adequate circulation in subjects with left ventricular dysfunction.

TABLE XVII. *Haemodynamic variables before and after insertion of the left ventricular assist device*

	Before insertion	After insertion
Systolic AP (mm Hg)	127	127
Diastolic AP (mm Hg)	75	82
CVP (mm Hg)	8.6	8.8
PCWP (mm Hg)	10.6	11.6
PAP (mm Hg)	20.3	27
HR (beat min^{-1})	79	98
CO (litre min^{-1})	5.66	7.6
LVAD flow (litre min^{-1})	0	5.7

Br. J. Anaesth. (1989), **63**, 244–247

CORRESPONDENCE

NON-FATAL PARADOXICAL AIR EMBOLISM

Sir,—Cerebral air emboli are usually fatal or may cause serious neurological conditions. The risk of such an embolus during insertion of a central venous catheter (CVC) is well recognized [1]. We report a patient in whom an embolus occurred when a three-way tap on a CVC became accidentally disconnected.

The patient was a 33-yr-old man with acute myeloid leukaemia who was receiving treatment via a permanently located CVC in the right internal jugular vein. The leukaemia was in good remission and the patient was cutting the lawn when he suddenly felt unwell, with sweating, dizziness and palpitations. The patient's wife heard a buzzing sound under his shirt and thought it was a bee. He then collapsed and had convulsions accompanied by blood streaming from the CVC.

On reaching the casualty department, it was imposible to establish verbal contact with the patient. He had flexion spasms of all extremities every 5–10 s, more marked on the left. Both pupils were dilated moderately, equal and reactive to light. Bilateral foot clonus was observed and his heart rate was 140 beat min^{-1}. Arterial blood-gas analysis revealed slight hypoxia with Pa_{O_2} 8.6 kPa, and Sa_{O_2} 90%.

The patient was treated with oxygen, a left lateral tilt, Diazemuls 45 mg i.v. and phenobarbitone 200 mg i.v. The seizures stopped, but no response could be obtained from the patient. After observation for 5 h he awoke suddenly and was neurologically completely intact.

Venous air embolism with CV catheters can occur when a subject is in an upright position. This has been demonstrated in 30–40% of patients who undergo neurosurgery in the sitting position [1]. The surest method of determining the diagnosis is by Doppler ultrasound [2]. Our patient presented with the signs of a cerebrally-triggered attack; air may have entered the cerebral circulation, possibly via a patent foramen ovale, which is present in 20–30% of the population. Previous instances of paradoxical air embolus via the foramen ovale have been described [3,4], and a pressure gradient of only 4 mm Hg is necessary to produce a right-to-left intracardiac shunt [5]. It has been shown in animals that the presence of air alone in the right atrium is enough to cause such a shunt [6], and this is seen especially when a bolus of air is involved [7].

Cerebral air emboli often result in serious neurological conditions [4], but in this patient there were no sequelae. Should brain damage occur, the treatment is limited. One patient has been described [8] in whom treatment with barbiturate-induced coma, slight hypothermia and hyperventilation were thought to have been effective. Hyperbaric oxygen treatment has also been described [9]. In the present patient complete recovery occurred without treatment.

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SEDATION FOR ENDOSCOPY

Sir,—We note with concern the paper by Boldy and coworkers on sedation for endoscopy [1]. In the results section, the authors state that "There were no cardiorespiratory problems in either group." There is no mention of any monitoring used in this study or at what times measurements or observations were made.

Cardiorespiratory changes during sedation for endoscopy are well known. Several studies have shown ECG changes during sedation and insertion of an endoscope [2–5], and significant reductions in oxygen tension have been demonstrated after introduction of the endoscope alone, after sedation with a benzodiazepine and after a combination of benzodiazepine and opioid [6–11]. Midazolam alone has been shown to cause marked respiratory depression [12].

We have completed a study of cardiorespiratory changes in 20 patients undergoing prolonged endoscopy. Data were recorded continuously by an Atari 1040 ST micro-computer, from ECG lead CM5, a pulse oximeter (Ohmeda Biox 3700), and a non-invasive arterial pressure monitor (Datascope). Sedation was provided by pethidine 25–50 mg and midazolam titrated to effect (mean dose 8 mg). The study commenced before administration of the sedative and continued for the first 1 h of recovery.

Oxygen saturation decreased in all patients (min 82%, SEM 12.5%), remained so for the duration of the examination and persisted into the recovery period. At the end of the study, saturation had not returned to baseline in 11 patients. An Sa_{O_2}

of 42 % was recorded in one patient. Sixteen of the 20 patients developed tachycardia. Ten patients developed supraventricular ectopic beats, ventricular ectopic beats or both. ECG changes resolved during the recovery period. A significant correlation was found between the occurrence of S-T segment depression and hypoxia ($r = 0.818$, $P < 0.00005$). No correlation was found between S-T segment depression and arterial pressure, heart rate or rate–pressure product.

From the results of our study and those of others, cardiorespiratory monitoring would appear to be mandatory during upper gastrointestinal endoscopy, especially if opioid analgesics are administered, hypoxia exists already or the patient is in a high risk group.

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Glasgow

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Sir,—We read with concern the paper by Boldy and colleagues [1], which seems to highlight much of the misunderstanding concerning the use of i.v. sedation. The authors do not provide details of patient weight, making it difficult to be precise concerning doses used. If we assume that the mean male weight was approximately 70 kg, the mean dose of midazolam used in males was 0.16 mg kg^{-1}. The manufacturer's recommended dose is 0.07 mg kg^{-1} for sedation during endoscopy—a dose found to be satisfactory by the second trial from the Hammersmith group [2] (not quoted by Boldy). As midazolam has approximately twice the hypnotic activity of diazepam, it seems unreasonable to compare diazepam 0.15 mg kg^{-1} with midazolam 0.16 mg kg^{-1}, and hardly surprising that, after endoscopy, patients were more sedated after midazolam.

Five milligrams is the maximum dose of midazolam we use, as the average patient is too profoundly sedated to be cooperative after being given midazolam 10 mg i.v. Bell and colleagues [3,4] showed significant decreases in oxygen saturation (to less than 80 %) during sedation with a benzodiazepine, exacerbated by passage of the gastroscope, and although they used larger doses (means of 6.7 and 6.3 mg) than we would recommend, these were considerably short of the doses of midazolam used by Boldy and colleagues. The addition of opioids to benzodiazepines compounds respiratory depression and hypoxia [5]. We believe that opioid supplementation has no place in sedation for routine upper gastrointestinal endoscopy.

As the peak effect of benzodiazepines given as a single i.v. injection occurs after 2–3 min, "titration" by injecting to a given endpoint cannot take this into account unless this time period is observed between each incremental dose.

The pharmacokinetics of midazolam make it better suited than diazepam to sedation for endoscopy and its superior amnesic properties provide an added clinical benefit. The recent availability of flumazenil, a specific benzodiazepine antagonist, obviates Boldy's assertions that midazolam-induced amnesia is a disadvantage. Antagonism of midazolam 5 mg with flumazenil 0.5 mg i.v. prevents further amnesia, reverses sedation and returns psychomotor variables to normal within 1 min [6]. In all published trials, there has been no clinically significant residual sedation caused by the disparity between the half-lives of the two drugs (57 min cf. 1.3–2.2 h). Of course, when excessive doses of midazolam are used in individual patients, this possibility may be increased.

R. C. Pearson
R. F. McCloy
Manchester

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Sir,—Thank you for the opportunity of responding to the letters from Drs Pearson and McCloy, and Drs Murray and Kenny.

Pearson and McCloy make a number of criticisms of our paper [1]. They believe that the dose of midazolam was excessive. In our study, started in 1983, midazolam was administered according to the data sheet recommendations at that time: "Midazolam should be given by slow intravenous injection until the patient becomes drowsy, speech becomes thickened and slurred, but the response to command is still maintained." In no case did the patient become unconscious or unable to follow commands. When we broke the code the dose of midazolam used was higher than anticipated, although similar to that used by Bardhan and colleagues [2] and by Bullimore and colleagues [3], and much less than the 15 mg used by Jensen, Knudsen and Kirkegaard [4]. Only healthy patients aged less than 75 yr entered the study (excluding those requiring regular sedation, who may need up to 60 mg of diazepam (the equivalent of midazolam 30 mg) to produce sedation [5]). We agree with Pearson and McCloy that a titrated dose may lead to a higher dose than is required for amnesia [6].

The object of our study was to compare a titrated dose of midazolam with a small fixed dose of diazepam and pethidine, rather than to compare equivalent doses of benzodiazepines. This has been undertaken elsewhere [3,6]. We accept that over-sedation may lead to a more difficult endoscopy. In our study, the endoscopist found no difference between the groups. Flumazenil was not available when the study was performed. We agree that it can overcome amnesia, but at high expense.

In our study, 88 % of the midazolam group and 86 % of the diazepam group indicated they would be happy to have a further endoscopy. Using low dose midazolam, 24–36 % of patients had no amnesia, 28 % gagged, 26 % coughed and 20 % retched. Therefore we do not agree that low dose midazolam should be used in all patients. When we tried low dose midazolam, we had several serious complaints from patients who had no amnesia and little sedation; this is similar to our experience using no sedation [7]. However, we shall conduct a trial of low dose midazolam against diazepam and pethidine.

The authors suggest that pethidine should not be used in endoscopy. The reference given by Pearson and McCloy does not support this statement. Rozen demonstrated hypoxia during endoscopy with opioids, especially in the elderly [8]. Murray and Kenny demonstrated hypoxia during endoscopy with midazolam and pethidine in small numbers of patients. This is not surprising, as hypoxia occurs during endoscopy without sedation [9,10], with diazepam [10], midazolam [11], and diazepam and pethidine [8]. There was no difference in hypoxia in a study comparing diazepam with pethidine and diazepam [10]. We agree that pethidine should not be used in older patients, but think that there is a case for its use in combination with diazemuls in younger patients likely to tolerate endoscopy badly.

Murray and Kenny asked about monitoring during endoscopy. There has been much correspondence on this topic [12–14]. We followed the British Gastroenterologists' Society guidelines [12] with two nurses present, one to assess the patient. We feel that there is not an indication for routine monitoring of arterial oxygen saturation or ECG. Endoscopy is relatively safe and there have been no serious complications of routine endoscopy at this hospital over the past 10 yr, with more than 1000 endoscopies performed each year. Cardiac arrest has been reported elsewhere, with an incidence of 0.008 % [15]. Careful selection of patients, and the use of oxygen for those at risk [16] is more important.

A. M. Hoare
D. A. R. Boldy
High Wycombe

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VENTILATION REQUIREMENTS DURING CAESAREAN SECTION

Sir,—I was interested to read the paper by Rampton and colleagues [1] on increased ventilation requirements during obstetric general anaesthesia. Their approach is ingenious for establishing the correct fresh gas flow (FGF) by adjusting this for each patient until the desired $P\mathrm{E}'_{\mathrm{CO_2}}$ is achieved. However, as they observed, this leads to frequently-adjusted flow rates in the short period before delivery. Are they justified in concluding that pre-delivery FGF rates should be higher than the post-delivery FGF?

In a similar study using the ADE system during anaesthesia for Caesarean section [2], we used a constant FGF throughout the study period. We had expected to find a change in $P\mathrm{E}'_{\mathrm{CO_2}}$ reflecting a change in FGF requirements following delivery, but on reviewing the hard copy trace of the $P\mathrm{E}'_{\mathrm{CO_2}}$, no evidence of an abrupt or gradual reduction was apparent following delivery. This is not surprising if one considers that the increase in ventilatory requirements in pregnancy can persist for as long as 14 days post-partum. Therefore, it would seem unnecessarily complicated to advocate two different FGF during Caesarean section.

P. W. Duncan
Preston

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Sir,—Thank you for the opportunity to reply to Dr Duncan's letter. He wonders if we were justified in recommending higher fresh gas flow (FGF) rates before delivery than after delivery. The major importance of the FGF is in regard to the fetal status before delivery. We quoted a post-delivery value ($109\ \mathrm{ml\ kg^{-1}\ min^{-1}}$) as stable $P\mathrm{E}'_{\mathrm{CO_2}}$ and FGF were always obtained, whereas in the much shorter induction-to-delivery interval we obtained a reasonably stable $P\mathrm{E}'_{\mathrm{CO_2}}$ of 4 kPa in only 50% of the patients, and thus cannot recommend our pre-delivery FGF ($121\ \mathrm{ml\ kg^{-1}\ min^{-1}}$) with such certainty. We were not suggesting that it would be obligatory to alter the FGF after delivery, as small changes in $P\mathrm{E}'_{\mathrm{CO_2}}$ are of little importance to the mother after the baby has been delivered.

Maternal hyperventilation may indeed persist for up to 14 days post-partum, but we feel that there may be an immediate reduction in ventilatory requirements after delivery, mainly because of removal of the fetus and placenta, and partly perhaps as a result of a deeper level of anaesthesia. The oxygen consumption of the human fetus at term is estimated to be $8\ \mathrm{ml\ kg^{-1}\ min^{-1}}$, and placental oxygen consumption varies from $10\ \mathrm{ml\ kg^{-1}\ min^{-1}}$ to half that of the fetus [1]. Thus the oxygen consumption of an average weight fetus and placenta at term might be in the region of $33\text{–}42\ \mathrm{ml\ min^{-1}}$, which is a significant proportion of the average oxygen consumption of mothers at term ($250\text{–}350\ \mathrm{ml\ min^{-1}}$).

A. J. Rampton
London

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BOOK REVIEWS

Fluids, Electrolytes and Acid Bases. Edited by G. T. Shires. Published (1988) by Churchill Livingstone Inc., Edinburgh. Pp. 203; indexed; illustrated. Price £27.50.

The first volume of *Clinics in Critical Care Medicine*, entitled *Acute Renal Failure*, was published in 1980. Since that time a further 13 volumes have been produced, covering a wide variety of subjects devoted to both adult and paediatric critical care medicine. The popularity and reputation of this series owes much to the transatlantic editorial format and the high quality of some of the earlier volumes. This high standard has not been reproduced consistently in subsequent issues.

Fluids, Electrolytes and Acid Bases is the 15th volume in the series. Its editor has commissioned contributions from a number of other well known surgical investigators. The subject material can be divided into three main sections which contain 11 chapters in just over 200 pages. Sections 1 and 2 deal with the general principles governing the physiology and pathophysiology of fluids and electrolytes and acid–base balance. The information provided in these sections can be found in many of the currently available standard texts, although few include such detail in as clear and concise a fashion. The third section covers the diagnosis and management of specific pathological clinical states and reflects the overall surgical emphasis of the book. Excellent chapters address the experimental and clinical rationale behind the treatment of haemorrhagic and burn shock. These are succeeded by a brief account of the use of prophylactic antibiotics in surgical practice (chapter entitled "Sepsis") and a discussion of the pharmacological and mechanical means of cardiac support (chapter entitled "Cardiogenic Shock"). These contributions seem misplaced in a book on fluid, electrolytes and acid–base balance, and suffer from a general paucity of detail. This is followed by a chapter on the "Endocrine Response to Haemorrhagic Shock" which is an interesting review of the interstitial space and an analysis of the complex neuroendocrine mechanisms responsible for blood volume restitution following haemorrhage. It might have been more appropriate for this to have preceded the contribution on haemorrhagic shock. The concluding chapter, on "Nutritional Needs", is a competent review of the metabolic response to injury and includes a widely accepted view on how judicious nutritional management can prevent some of the deleterious effects of this response.

D. A. B. Turner

Lectures in Anaesthesiology 1988/1, 1st Edn. Edited by J. S. M. Zorab and R. Weller. Published by Blackwell Scientific Publications in association with W.F.S.A., Oxford. Pp. 102; illustrated. Price £10.00.

Lectures in Anaesthesiology are to be a series of "inexpensive, twice yearly publications containing a collection of lectures of interest to Anaesthesiologists". They are to be published by the World Federation of Societies of Anaesthesiologists (W.F.S.A.) and this is the first, containing nine lectures. The Editor in Chief and the Associate Editor are both British; of the Consulting Editors, one is Australian, one South African and one is from the U.S.A. Of the contributors to the present volume, one is Chinese, four are British, two are South African and one Australian.

Professor Yung is from the People's Republic of China. His contribution is in two parts. In the first he gives some indication of the progress of the specialty in China in recent years. Recent advances are outlined, such as the introduction of pulmonary artery catheterization and labetalol. The reader is left with the impression that it would have been more interesting if a state-of-the-art view of the whole of China had been given,—the worst in addition to the best. This seems to be an opportunity lost. The second part of Professor Yung's contribution is an account of i.v. procaine balanced anaesthesia, which is gaining in popularity in China.

Boulton and Lee deal mainly with draw-over anaesthesia with ether, in two chapters. This gives a good summary of the subject which might well appeal to many outside such countries as the United Kingdom. However, it can hardly be said to be particularly topical.

The British R.A.F. contributes two chapters. Merrifield gives a clear and useful account of oxygen concentrators and McLaren an interesting account of the somewhat esoteric subject of aeromedical evacuation. James writes on magnesium and anaesthesia, a specialized subject mainly of interest to the intensivist. A chapter on pharmacokinetics does little to elucidate the subject and the last chapter, on pulmonary ventilators, is an over-simplification.

Reviewers, on the whole, are both supercilious and destructive. One is sometimes tempted to extend the Shavian aphorism to "He who can, does. He who cannot, teaches. He who can neither do, nor teach, reviews and criticizes." However, the present reviewer feels bound to say, with some diffidence, that this really is not a very good book.

The series is intended for those "who may not have access to regular, continuing education," but the plan has somehow gone wrong. Some of the subjects seem too sophisticated, and the treatment of others too complicated. The whole lacks any form of coherence. Yet the idea behind it must be a good one. One can only hope the series improves.

J. E. Utting

Pediatric Cardiac Anesthesia, 1st Edn. Edited by C. L. Lake. Published by Appleton and Lange, Connecticut. Pp. 452; indexed; illustrated. Price £69.55.

This is one of the best anaesthetic books I have read recently, and I thoroughly enjoyed reading it, despite the rather small typeface. Its 22 chapters are written by senior anaesthetists and paediatricians from the United States, with one contributor from Canada, and the product reflects the wide-ranging expertise found in this area in Charlottesville, Philadelphia, Pittsburgh, Birmingham, Atlanta and elsewhere in North America.

There is plenty of practical and detailed advice which is applicable on both sides of the Atlantic, and a refreshing commonsense approach throughout. The opening chapters on the history of paediatric cardiac anaesthesia and the pathophysiology and embryology of congenital heart disease are followed by helpful chapters on preoperative evaluation, catheterization, perioperative management, monitoring (a realistic and pragmatic approach), and pharmacology. This last chapter will be of value to all involved in paediatric anaesthesia, cardiac or non-cardiac. These are followed by a chapter on extracorporeal circulation and a particularly informative and comprehensive one on myocardial preservation. There follow chapters on all the main congenital cardiac anomalies with their anaesthetic implications, and the book closes with chapters on general intensive care and postoperative respiratory and cardiac management.

There are of course areas that one may criticize, although it would be churlish to exaggerate them. It would have been interesting to read of the organization of paediatric cardiac anaesthesia, and the chapter on cardiac catheterization, written by two cardiologists, says little on anaesthetic management, blood loss or postoperative care. Surely it is important to know the indications for general anaesthesia rather than sedation, especially for the newer interventional techniques. Doses related to weight in pounds and kilograms appear in different sections of the same table (20.3). If our American colleagues cannot be persuaded to go metric, at least they should be consistent. Failure to mention fresh frozen plasma under blood products seems a surprising omission, and there is unnecessary overlap between the postoperative care chapters.

Despite these relatively minor criticisms, this is a book which can be recommended wholeheartedly. Those involved in this field should put it high on their list of priorities for individual purchase, and all major anaesthetic libraries should possess a copy. I hope that, if this book runs to a second edition, which it surely will, the editor will persuade the publishers to improve the quality of the paper and the size of the print.

D. J. Hatch

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

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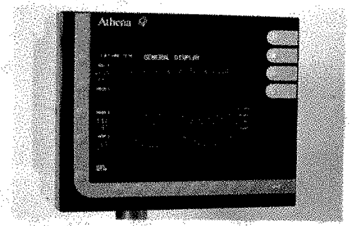

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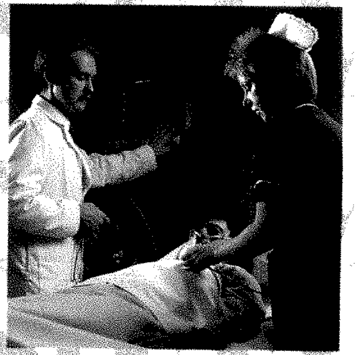

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EDITORIAL

EXTRADURAL OPIOIDS IN LABOUR

With the discovery of opioid receptors in the spinal cord [1] and of the undoubted efficacy of opioids given by the extradural route [2], this technique of analgesia rapidly became popular and obstetric anaesthetists were not slow to adopt the method. During the early days we had hoped optimistically that this route of administration would provide analgesia which was complete, long lasting and free from the side effects produced by systemic opioids and extradural local anaesthetics. First began the search for the ideal drug: when used in obstetrics, morphine was soon found to be unique in its capacity to produce more side effects than analgesia [3]. Although effective in the management of chronic pain [2], this polar opioid penetrated meninges too slowly to be of value via the extradural route for labour. Because of the large doses that are necessary, pethidine owes part of its action to a local anaesthetic effect, and it has a shorter duration of action when given extradurally than i.m. [4, 5]. In the U.S.A., butorphanol has been given extradurally, and it produces profound somnolence [6, 7]. In labour, only fentanyl [8–13] and sufentanil [14–16], when added to bupivacaine, have been shown to produce analgesia that is quicker in onset, more intense and longer lasting than bupivacaine alone. However, in general fentanyl and sufentanil are unreliable when used alone [17] and no better than bupivacaine alone [18].

It is not surprising that the combination of fentanyl and bupivacaine produces greater analgesia than the same dose of each agent used independently. It is unnecessary to invoke potentiation to explain this finding. If fentanyl is added to a dose of bupivacaine expected to be effective alone, not only are the subjective benefits of each agent likely to be less, but this approach cannot avoid local anaesthetic induced side effects of weakness, hypotension and poor expulsive efforts. Moreover, with the passage of time it has become clear that extradural opioids have individual side effects, although the only significant one in labour is pruritis, which is a consistent observation. Some anaesthetists have obtained good results by adding fentanyl 80–100 μg to a bupivacaine test dose of 10–12 mg [8–10], while others, whilst exploring various combinations, have found an optimum dose of fentanyl 50 μg in combination with bupivacaine 25 mg [11, 12]. Even with the optimal regimens, the benefits of the combination are found to be only marginal in comparison with the individual agents, and the duration of action is not as great as had been hoped.

Continuous extradural infusions avoid inadequate duration of action, and the peaks of side effects and troughs of analgesia, which occur with intermittent bolus injections. However, a recurring problem with this technique is that either the infusion rate is too slow and top-ups, albeit fewer, are required to maintain analgesia, or the infusion rate is too rapid, with an increase in total dose of local anaesthetic resulting in increase in the height of the block; motor block, hypotension, systemic toxicity and instrumental delivery are also more likely to occur. This may be obviated by avoiding the use of a fixed infusion regimen and training midwives to use regular dermatome testing and to modify the infusion rate according to the needs of each mother [19]. Another strategy is to add fentanyl to the infusion. Skerman and colleagues [20] examined the effect of a bupivacaine bolus followed by infusion of 0.125 % at 10 ml h^{-1} with and without fentanyl, while Chestnut and colleagues [21] halved the dose of bupivacaine when fentanyl was added. More recently, D'Athis and colleagues [22] compared an intermittent dose regimen with that of a bolus followed by infusion of 3 ml h^{-1} of a combination of 0.25 % bupivacaine with fentanyl 5 μg ml^{-1}. All these studies found that the infusion of the combination was the more reliable treatment. In the present issue of the Journal, Dr Jones and her colleagues [23] have compared a fixed dose regimen of a bupivacaine bolus and infusion, with and without fentanyl. They used a generous test dose of lignocaine and, following the loading dose of bupivacaine, gave supplements in order to achieve block of the T10 dermatome irrespective of the mother's symptoms. As would be expected, fewer supplements were needed in the group receiving fentanyl with bupivacaine; with the high catheter placement used, perineal pain was a common reason for administration of supplements. In common with other studies [8–10], it was found that neither hypotension nor abnormal deliveries were avoided by the use of fentanyl, although with the fairly large dose of bupivacaine used by this Scottish group, this was perhaps not surprising.

What, then, is the current status of extradural opioid analgesia in labour? Undoubtedly, it can reduce the dose requirements for bupivacaine and enhance analgesia from an extradural infusion. However, hypotension and instrumental deliveries are not avoided, while a new side effect, pruritis, is introduced. The use of an opioid can only be advantageous if it allows the use of minimal doses (10–12 mg) of bupivacaine; even so, it is questionable if the gain in enhanced analgesia outweighs the inconvenience of using a controlled drug. However, there are two distinct advantages: improved management of perineal pain [17], where an opioid in the lumbar region is well placed to gain access to its site of action in the spinal cord, whilst a dose of local anaesthetic sufficient to reach the sacral roots is likely to produce profound motor block of lumbar roots; and effective management of that well-known problem of obstetric extradural block, shivering [24, 25].

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Br. J. Anaesth. (1989), **63**, 254–259

COMPARISON OF BUPIVACAINE AND BUPIVACAINE WITH FENTANYL IN CONTINUOUS EXTRADURAL ANALGESIA DURING LABOUR

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SUMMARY

In a randomized, double-blind study of 39 mothers in labour, we have compared a loading dose of 0.5% bupivacaine 6.0 ml and fentanyl 100 µg given extradurally, followed by an infusion of 0.08% bupivacaine 15 ml h^{-1} plus fentanyl 37.5 µg h^{-1}, with a loading dose of 0.5% bupivacaine 6.0 ml and saline 2.0 ml, followed by an extradural infusion of 0.08% bupivacaine alone, per hour. Analgesic levels were more consistent and sustained in mothers who received fentanyl in addition to bupivacaine, and the duration from the time of the loading dose to the first top-up was extended considerably in this group. The only significant side effect was a high incidence of mild pruritus in the fentanyl group. The addition of fentanyl to the extradural loading dose and subsequent infusion of local anaesthetic is a satisfactory alternative to giving higher doses of local anaesthetic alone.

Extradural block by intermittent bolus injection of local anaesthetic provides satisfactory analgesia in labour. This technique, however, is not ideal and has a number of disadvantages [1]. Variation in the degree of sensory, motor and sympathetic nerve block may cause painful intervals, variation in muscle power and cardiovascular instability. There are also risks of inappropriate catheter placement or migration of the catheter from the extradural to an intrathecal or i.v. site. Theoretically, slow infusion of local anaesthetic is safer than an intermittent bolus technique [1–3].

Continuous extradural infusions have been used to provide background analgesia during labour, but supplementary bolus doses and top-ups may be required [2–9]. Progressively increasing the dose of local anaesthetic infused reduces the frequency of supplementary top-ups, but increases the risk of systemic toxicity and unacceptable sympathetic [2] and motor block, and increases the likelihood of failure to progress in second stage and subsequent operative delivery [10–12].

When used alone, extradural opioids have been unsuccessful in providing analgesia in labour [13–19]. However, this technique produces good postoperative analgesia when used either alone or in combination with local anaesthetic by bolus dose or infusion [20–23]. The addition of fentanyl to an extradural loading dose of bupivacaine has been shown to augment the duration of analgesia [18, 20, 24].

This study was performed to observe the effect of adding fentanyl to a loading dose of plain bupivacaine and to the subsequent infusion of 0.08% plain bupivacaine given extradurally at a rate of 15 ml h^{-1}.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee, and written informed consent was obtained from all participants. Primiparous and multiparous mothers were included in the study, provided the remaining labour was anticipated to be more than 3 h duration. Not all mothers were

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This article is accompanied by an Editorial.

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in established labour, as some with mild hypertensive disease of pregnancy were included and extradural analgesia was commenced immediately before artificial rupture of the membranes and induction of labour by i.v. infusion of syntocinon. No parturient received opioid analgesia before extradural block.

The extradural catheter was inserted at the first lumbar interspace with the parturient in the lateral position. Loss of resistance was detected with not more than 5.0 ml of saline and 2–3 cm of an end-hole catheter was inserted in the extradural space. All parturients received a standard test dose of 2.0% lignocaine 4.0 ml.

The parturients were allocated randomly to one of two groups. Group F received a loading dose of 0.5% bupivacaine 6.0 ml with fentanyl 100 µg (2.0 ml) and group B received a loading dose of 0.5% bupivacaine 6.0 ml with saline 2.0 ml. The loading dose was given 10–15 min after the test dose. Immediately after the loading dose, group F received an extradural infusion of 0.08% bupivacaine 15 ml h^{-1} with fentanyl 37.5 µg h^{-1}, and group B received 0.08% bupivacaine 15 ml h^{-1} alone.

The anaesthetist performing the block made up the loading doses and the infusions; the latter were prepared in a 120-ml graduated burette. To prepare 0.08% bupivacaine, two ampoules of 0.5% bupivacaine 10 ml were added to the burette and this was diluted to 120 ml with 0.9% saline. In the case of the fentanyl infusion, fentanyl 300 µg was added before making up the solution to 120 ml. Neither the assessor nor the parturient was aware of the group allocated. All extradural fluids were infused by a volumetric pump (IMED 927) via a micro-bacterial filter. The volume infused was checked hourly by the midwife in attendance. Posture of the parturients was not controlled strictly, but most assumed a semi-recumbent position tilted to the right or left side alternately.

The level of sensory block and degree of motor block were assessed at 30 min following the loading dose. The analgesic level was defined as the upper dermatomal level with diminished sensation to pinprick. Motor block was assessed on the Bromage scale [25]. The sensory block 30 min after the loading dose was accepted if the analgesic level reached T10 bilaterally. If not, a supplementary dose of 0.5% bupivacaine 2.0 ml was given for each segment unblocked, on each side, below T10. The parturient was re-assessed after a further 30 min and, if the block reached at least T10 bilaterally, the parturient was included in the study. Heart rate and arterial pressure were recorded by the midwife at 30-min intervals, and rate of ventilation every 60 min. Assessment was carried out at intervals until the first top-up was requested. When a top-up was requested because of pain, the analgesic level and motor block were assessed immediately before and 30 min after the top-up. A standard top-up of 0.25% bupivacaine 10 ml was used. An additional bolus was given if analgesia remained unsatisfactory at 30 min following a standard top-up or to cover the extra analgesic needs of an operative delivery. The extradural infusion was continued until delivery of the baby or until the establishment of more intense block for Caesarean section.

Side effects were noted during the course of the infusion, including: arterial hypotension (systolic less than 95 mm Hg), respiratory depression (rate of ventilation less than 12 b.p.m.), nausea and vomiting, difficulty with micturition, urinary catheterization and pruritus. Details of the mode of delivery and condition of the infant were recorded. The following day, the mothers were asked to complete visual analogue scales to provide subjective assessment of analgesia and sedation.

Statistical analysis was performed using Chi-squared test or Wilcoxon rank sum test. The intervals from the administration of the loading or supplementary dose to the first top-up were subjected to survival analysis using Cox's proportional hazards model and log rank tests.

RESULTS

Forty-five parturients were entered into the study, but six were excluded as labour was complete within 3 h. Of the remaining 39 parturients, 20 received bupivacaine plus fentanyl (group F) and 19 received bupivacaine alone (group B). There

TABLE I. *Demographic data of groups F and B (mean (SD)). No significant difference between groups (Wilcoxon rank sum test)*

	Group F	Group B
Number	20	19
Primiparous	14	15
Age (yr)	26.35 (4.88)	25.32 (6.15)
Weight (kg)	73.77 (12.3)	78.14 (11.46)
Height (cm)	163.0 (7.95)	163.26 (6.82)
Gestational age (wk)	39.9 (2.6)	40.05 (0.97)

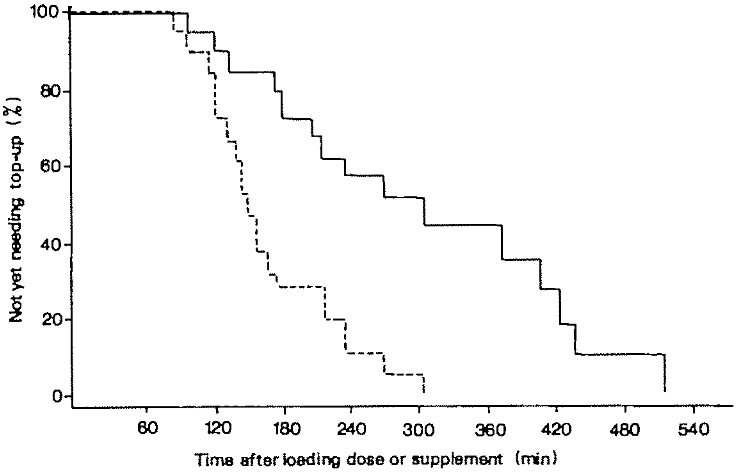

FIG. 1. Cumulative proportion of patients continuing without top-up. --- Group B; —— Group F.

were no differences in the demographic data of the two groups (table I). In group F, 17 mothers were in the first stage of labour when extradural analgesia was requested. Three requested extradural analgesia before induction of labour by artificial rupture of the membranes and i.v. infusion of syntocinon. The corresponding numbers in group B were 13 and six. Cervical dilatation at the time of establishment of the extradural block did not differ between the two groups (Chi-squared test).

Survival analysis was used to compare the duration of analgesia in the two groups, following the loading dose or supplementary dose which achieved an analgesic level of T10 bilaterally. The duration was defined as the time of the loading dose or supplementary dose to the time of the first top-up or delivery. The cumulative proportion surviving is presented in figure 1; the difference between the groups is statistically significant ($P < 0.001$). The median survival time of group F was 303 min and of group B was 150 min. No parturient in group F required a supplement to achieve a bilateral analgesic level of at least T10, whereas four parturients in group B required a single supplementary dose (range 2–10 ml). This was not significant (Chi-squared). Twelve parturients (60 %) in group F and nine (47 %) in group B delivered after one or no top-ups (excluding top-ups given for operative delivery) (ns, Chi-squared). There was no difference between the groups in the duration of first and second stages of labour and the time from the loading dose to delivery (Wilcoxon rank sum test).

The analgesic level increased and decreased in both groups. Inequality of the analgesic level between the sides of the trunk was seen in both groups and attributed to the effect of posture during the extradural infusion; there was no significant difference between the two groups.

No parturient in either group experienced complete motor block. One parturient in each group had motor block such that they could move only the feet (Grade 2 Bromage scale). This occurred approximately 30 min after the loading dose in each case and motor power improved progressively during the infusions. Most parturients in each group retained normal power throughout the duration of the infusion. The mean infusion time was 6 h 34 min (maximum 12 h 24 min) in group B, and 7 h (maximum 11 h 55 min) in group F.

The dose range of bupivacaine in group B was 18.0–39.16 mg h^{-1} and in group F was 16.0–31.18 mg h^{-1}. There was a significant difference between the mean dose of group B (25.93 mg h^{-1}) and group F (21.32 mg h^{-1}). The maximum dose of bupivacaine was 241.44 mg during an infusion of 11 h 40 min. These values include the loading dose, initial supplements where given and subsequent top-ups. They do not include additional doses of bupivacaine given for operative delivery.

No evidence of systemic toxicity was noted.

The mean dose of fentanyl given, including the loading dose, in group F was 51.08 μg h^{-1}, giving a mean dose of 357.43 μg per labour. The maximum dose of 547 μg was given over a labour of 11 h 55 min duration. No evidence of respiratory

TABLE II. *Frequency (number (%)) of side effects in groups F and B. Significance was tested by Chi-squared*

	Group F	Group B	*P*
Number	20	19	
Hypotension (SAP < 95 mm Hg)	4 (20)	2 (10)	ns
Respiratory depression	0	0	ns
Nausea	9 (45)	6 (32)	ns
Vomiting	7 (35)	4 (21)	ns
Difficulty passing urine	9 (45)	11 (58)	ns
Catheterization	9 (45)	13 (68)	ns
Pruritus	15 (75)	1 (5)	< 0.001

TABLE III. *Mode of delivery in groups F and B. There was no significant difference between groups (Chi-squared)*

Mode of delivery	Group F	Group B
Spontaneous vertex delivery	8	5
Forceps	4	9
Lower segment Caesarean section	8 (40 %)	5 (26 %)

TABLE IV. *Details of infants born to mothers in Groups F and B (median (range)). No significant difference between the groups (Wilcoxon rank sum test)*

	Group F	Group B
Birth weight (kg)	3.4 (2.4–5.1)	3.6 (2.4–4.5)
Apgar-minus-colour score		
1 min	8 (2–8)	8 (4–8)
5 min	8 (3–8)	8 (8–8)
Naloxone given (No. of neonates)	0	1

depression was observed in the mothers in this group.

The incidence of side-effects is recorded in table II. Fifteen parturients in group F (75 %) experienced pruritus, mainly above the analgesic level of the block; particularly over the breasts and occasionally involving arms and face. One parturient in group B (6 %) described pruritus associated with paraesthesiae during establishment of the extradural block. A high frequency of operative delivery was seen in both groups (table III).

There were no significant differences in the condition of the infants of each group (table IV). No infant in group F suffered respiratory depression requiring administration of naloxone. Analysis by visual analogue scales revealed a high degree of satisfaction with the analgesia provided by the technique of extradural infusion in each group. Drowsiness was not considered a problem, although it was experienced in both groups. There was no significant difference between the groups in terms of analgesia and sedation (fig. 2).

DISCUSSION

The addition of fentanyl to the loading dose of 0.5 % bupivacaine and to the subsequent infusion of 0.08 % bupivacaine given extradurally during labour significantly prolonged analgesia compared with bupivacaine alone. Justins and colleagues [18, 19] produced an increase in duration from loading dose to first top-up, by adding fentanyl 80 µg to bupivacaine 12 mg in the loading dose, during labour. However, this loading dose was not followed by a continuous extradural infusion of local anaesthetic. It is not possible to conclude from our study whether the increase in duration of analgesia observed is a result only of the addition of fentanyl to the loading dose or of the combination with the fentanyl infused. The loading dose in our study was bupivacaine 30 mg plus or minus fentanyl 100 µg in 8.0 ml of solution. This dose of bupivacaine alone was inadequate in some parturients (four of 19 in group B required supplementation) to provide analgesia to T10 bilaterally, whereas the addition of fentanyl 100 µg provided analgesia to T10 in all parturients. This more complete analgesia provided by the addition of fentanyl was observed by Justins' group [18, 19]. The addition of fentanyl to the loading dose appears to provide a suitable alternative to giving a greater mass of local anaesthetic in the loading dose, which may cause problems of high sympathetic block and arterial hypotension [26].

The commonest reasons for requesting additional analgesia were low back pain, and rectal or perineal pain. Of 34 parturients receiving a first top-up, 14 had blocks to T9 or above. This may

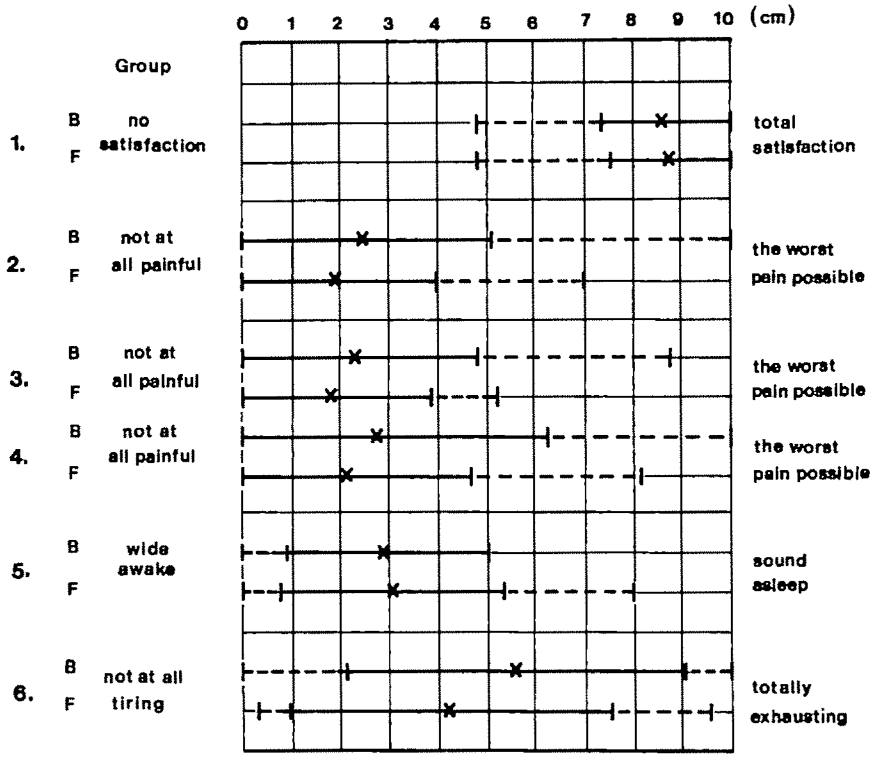

FIG. 2. Results of visual analogue scores. 1 = General satisfaction with technique of pain relief from the onset of the extradural until after delivery. 2 = How painful was it to have the extradural inserted? 3 = How painful was the first stage? 4 = How painful was second stage? 5 = How drowsy did you feel throughout labour? 6 = How tiring did you find pushing during second stage? (Not enquired of Caesarean sections.) x = Mean; — = SD; --- = range.

suggest progression of labour to involve unblocked sacral nerve roots.

Three parturients (two in group F and one in group B) exhibited a progression of analgesic level during the course of the infusion. This emphasizes the need for regular monitoring of sensory levels during extradural infusions.

Twelve parturients in group F and nine in group B delivered after a maximum of one top-up (excluding top-ups for operative delivery). Other studies have achieved a higher incidence of delivery on loading dose and infusion alone [5, 27–29]. Our observation of a requirement for additional top-ups may reflect our criterion for entry into the study of an anticipated labour exceeding 3 h.

Six parturients developed hypotension, five of whom had analgesic levels at or above T6. There was no difference between the groups. Hypotension occurred in five parturients at the time of the loading dose and in one (in group F) after a top-up. The observed stability of cardiovascular parameters, provided aortocaval compression is avoided, during extradural infusion of these dilute solutions of local anaesthetic is noteworthy.

A high frequency of operative delivery was observed in both groups. The overall annual frequency of Caesarean sections within the maternity units was 15% during the year of the study. The high overall frequency of 33% in this study may reflect the design of the study, which selected labours anticipated to be in excess of 3 h and, therefore, included a high proportion of primiparous patients.

There was no difference between the groups in the condition of the infants as measured by the Apgar-minus-colour scores [30]. There was no evidence of respiratory depression and only one neonate (in group B) received naloxone empirically, the mother not having received any opioid.

The technique of combining local anaesthetic and opioid deserves further study, as an appropriate combination may reduce to a minimum the need for subsequent top-ups during an extradural infusion in labour. The addition of a small dose of opioid to a loading dose of extradural local anaesthetic and its subsequent extradural infusion is an alternative to increasing the dose of local anaesthetic administered.

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Br. J. Anaesth. (1989), **63**, 260–265

ANALGESIA-INDUCED RESPIRATORY DEPRESSION: COMPARISON OF MEPTAZINOL AND MORPHINE IN THE POSTOPERATIVE PERIOD

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SUMMARY

Forty-nine patients undergoing elective total hip replacement received either morphine or meptazinol for postoperative analgesia from a patient-controlled analgesia apparatus. Ventilatory rate and volume and arterial oxyhaemoglobin saturation were recorded continuously for the first 24 h following surgery. Episodic hypoxaemia was seen in both groups, associated with disturbances in ventilatory pattern. There was no significant difference in the incidence or severity of observed hypoxia between the groups, or with respect to the class of ventilatory disturbance. Mean linear analogue scores for pain and nausea were significantly ($P < 0.05$*) greater in the meptazinol group than in the morphine group 8 h after operation, but did not differ significantly at any other time. The mean number of demands for analgesic drugs was similar in the two groups. The meptazinol group had a greater requirement for anti-emetic drugs than the morphine group (*$P < 0.05$*). It was concluded that meptazinol and morphine in equianalgesic doses had similar effects on ventilation in the postoperative period.*

Meptazinol has been shown to be an effective analgesic for moderate to severe pain when administered parenterally and has been compared favourably with other opioids given for postoperative analgesia [1]. A major advantage claimed for meptazinol is a relative lack of respiratory depression and its use after operation by i.m. injection [2] or i.v. infusion [3] has not been associated with hypercapnia.

The respiratory effects of analgesic drugs have been assessed previously by laboratory tests and intermittent measurements in clinical situations [4]. More recently, Catling and colleagues [5] compared i.m. injections with i.v. infusions of papaveretum using a respiratory inductance plethysmograph (RIP) and demonstrated episodic disturbances of ventilation which were more severe in the infusion group. Catley and colleagues [6] used RIP and ear oximetry to compare the effects of a morphine infusion with regional analgesia. They showed episodic hypoxaemia lasting 5–120 s in the majority of the patients receiving morphine, but not in those given regional analgesia.

The short duration of such episodes implies that they are likely to be missed by intermittent assessments of respiratory function. In addition, the occurrence of transient but profound hypoxaemia suggests that harm may occur in the absence of a generalized deterioration in respiratory function [7]. Comparisons of the respiratory effects of different analgesics, therefore, should include continuous monitoring.

A fair comparison of the respiratory effects of two analgesic drugs requires that they be given in equianalgesic doses. Patient controlled analgesia (PCA) has been used to achieve equivalent degrees of analgesia for meptazinol and pethidine given i.v. [8] and meptazinol and morphine i.m. [9].

We designed a double-blind study of the respiratory effects of morphine and meptazinol

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administered by PCA to patients following major orthopaedic surgery. Ventilation and oxyhaemoglobin saturation (Sa_{O_2}) were monitored continuously over a 24-h period in order to detect periods of hypoxaemia and to relate these to disturbances in ventilatory pattern.

PATIENTS AND METHODS

We studied patients aged between 50 and 80 yr and of ASA status I or II who presented for elective total hip replacement, after informed consent was obtained. Patients were excluded if they were more than 25% above ideal body weight, were already receiving opioid analgesic drugs, gave a history of intolerance or sensitivity to opioid analgesics, were unable to comprehend the nature of the assessments or the purpose of PCA or were unable to use PCA because of arthritis. Patients were excluded also if they gave a history of a sleep disorder.

The study was approved by the District Ethics Committee.

Patients were instructed before operation in the use of PCA and a detailed explanation of the study was given. Morphine 10 mg/70 kg and atropine 0.6 mg/70 kg were given by i.m. injection 1 h before operation. Anaesthesia was induced with thiopentone and, after neuromuscular block and intubation of the trachea, was maintained with nitrous oxide in oxygen supplemented by a volatile agent. Fentanyl 100 μg i.v. was available at the discretion of the anaesthetist.

The bolus dose of the PCA pump (Cardiff Palliator, Graseby Dynamics) [10] was set at 0.8 ml and the lock out period at 10 min. Patients were allocated randomly to receive either morphine 2.5 mg ml^{-1} or meptazinol 25 mg ml^{-1}. The bolus and maximum hourly doses, respectively, were thus 2 mg and 12 mg h^{-1} for morphine and 20 mg and 120 mg h^{-1} for meptazinol. The potency ratio of 10:1 for meptazinol and morphine was calculated from previous studies [2, 4]. The analogue output from the PCA pump was connected to a chart recorder in order to record the number of successful demands for analgesia. Cyclizine 50 mg was given i.m. for nausea and vomiting, at the discretion of the ward staff.

Ventilation was monitored with a simple quantitative RIP (GVT, P.K. Morgan) [11] and Sa_{O_2} with a pulse oximeter (Ohmeda Biox IIa or III) via an ear probe. The analogue outputs of both instruments were recorded continuously on a four-channel instrumentation tape recorder (Store 4 FM, Racal). A sequencer unit (Earth Data Ltd) enabled a complete 24-h recording to be made without continuous supervision, by reversing the direction of tape travel and changing the input channels when the end of the tape was detected. The recordings were subsequently transcribed onto a multi-channel chart recorder (W and W 406) for analysis after initial scrutiny on a storage oscilloscope (Gould 4040).

The patients were returned to the ward after a short stay in the recovery area. The PCA pump was connected through a non-return valve to a separate i.v. cannula and the patients reminded of the correct usage. Calibration signals from the oximeter were recorded on tape and the RIP and oximeter connected to the patient. Recording was commenced 2 h later to allow stabilization after anaesthesia and surgery. Supplementary oxygen was given at the discretion of the anaesthetist and the ward nursing staff. Note was taken of the time of its discontinuation.

Patients were assessed at 2, 4, 8, 16 and 24 h after operation by a sole independent nurse observer. A 10-cm linear analogue scale (LAS) and a five-point verbal rating scale (VRS) were used to assess the patient's pain at each assessment. Nausea, sedation and dizziness were assessed also using separate 10-cm LAS. Patients who were asleep at the time of assessment were not roused and no response was recorded. The overall efficacy of analgesia was rated using a four-point VRS at the completion of the study period.

Systemic arterial pressure and heart and ventilatory rates were recorded by the ward nursing staff at regular intervals. The occurrence of nausea or vomiting was documented, as was the frequency of administration of cyclizine.

Analysis of results

The records were analysed by a sole observer who was unaware of the analgesic given. The recordings of Sa_{O_2} were scrutinized and the periods when supplementary oxygen had been administered were excluded from the analysis. The number and duration of all periods of hypoxia were noted for each patient. Hypoxic episodes were subdivided into those in which Sa_{O_2} was between 85 and 90% and those with $Sa_{O_2} <$ 85%. In addition, any decrease in Sa_{O_2} of more than 4% occurring within a 20-s period was noted. The latter decreases were designated transient hypoxaemia, and both hypoxic episodes and

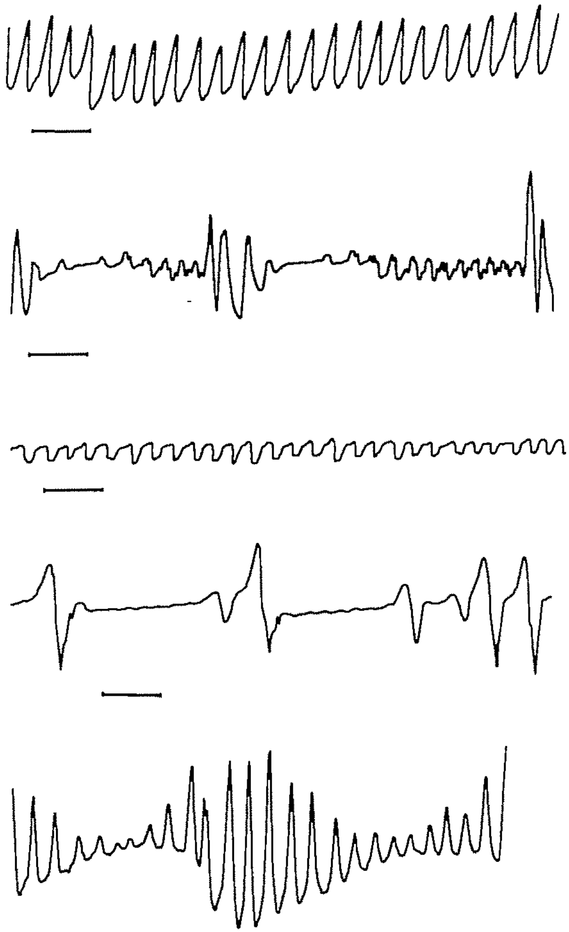

FIG. 1. Examples of ventilatory wave forms recorded with a GVT inductance plethysmograph. Redrawn for clarity. From the top: Normal ventilation, obstructive apnoea, partial obstruction, central apnoea and periodic ventilation. Horizontal bar represents 10 s. Recordings move from left to right.

transient hypoxaemia were related to the ventilatory pattern derived from the RIP at that time.

Abnormal ventilation could be distinguished from the normal by the shape of the ventilatory waveform. Partially obstructed breathing is associated with a characteristic "flat top" to the waveform, and complete obstruction results in a very low amplitude signal, followed by normal ventilation as arousal occurs. Central apnoea is characterized by the absence of ventilatory movement (fig. 1). Each hypoxic episode and transient hypoxaemia noted from the recording of Sa_{O_2} were classified into one of the following categories, designated as ventilatory events, on the basis of the simultaneous recording:

(1) *Obstructive apnoea*: a period of 15 s or longer of obstructed breathing terminated by arousal and normal deep breaths.
(2) *Obstructive pause*: an obstructive apnoea lasting between 6 and 14 s.
(3) *Partial obstruction*: a "flat topped" waveform indicative of obstructed breathing.
(4) *Central apnoea*: a period of 15 s or longer with no ventilatory movement.
(5) *Central pause*: a central apnoea lasting between 6 and 14 s.
(6) *Central hypoventilation*: a decrease in amplitude of the RIP signal to less than 50% of the initial value.
(7) *Periodic breathing*: a cyclically varying ventilatory signal with gradual increase and decrease in tidal volume.
(8) *Normal ventilation*: no change in RIP signal to explain the hypoxic episode or transient hypoxaemia.
(9) *Artefact*: movement artefact or other technical difficulty resulting in an RIP signal unsuitable for analysis.

Data were analysed by Student's *t* test if distributed normally, Wilcoxon rank sum test for the data derived from LAS and VRS and for the ventilatory data and Chi square and Fisher's exact test where appropriate.

RESULTS

Sixty-three patients were included in the study. The data from 14 were excluded subsequently because the total duration of recording technically suitable for analysis, but including periods when supplementary oxygen was given, was less than 18 h or long acting sedative drugs were administered during the anaesthetic. The demographic data for the 26 patients in the meptazinol group and the 23 patients in the morphine group were matched evenly for weight, height, sex and

TABLE I. *Demographic data and duration of recording without supplementary oxygen (mean (SEM)) in patients receiving morphine or meptazinol*

	Morphine	Meptazinol
Age (yr)	67.52 (1.48)	67.46 (1.54)
Weight (kg)	65.91 (2.04)	66.0 (1.54)
Height (m)	1.65 (0.021)	1.64 (0.018)
Sex	7M/16F	7M/19F
Duration of recording (h)	15.1 (0.74)	14.6 (0.75)

TABLE II. *Total duration of episodes of hypoxaemia (mean (SEM)) expressed as minutes per hour of recording.* n = *Number of patients with episodes of hypoxaemia*

	Morphine (min h^{-1})	Meptazinol (min h^{-1})	P
Sa_{O_2} 89–85 %	7.1 (2.1) (n = 22)	7.6 (2.4) (n = 21)	ns
Sa_{O_2} < 85 %	1.0 (0.8) (n = 11)	0.1 (0.05) (n = 6)	ns

TABLE III. *Number* (n) *and frequency of ventilatory events per hour of recording (mean (SEM)) related to hypoxaemia in patients receiving either morphine or meptazinol. OA = Obstructive apnoea; PO = partial obstruction; CA = central apnoea; CP = central pause; CH = central hypoventilation; PB = periodic breathing; NV = normal ventilation; AR = artefact. (See text for definitions)*

	Meptazinol		Morphine	
Event	n	Frequency	n	Frequency
OA	8	1.1 (0.6)	2	0.1 (0.1)
PO	11	0.5 (0.2)	15	0.4 (0.1)
CA	6	0.3 (0.0)	4	0.1 (0.0)
CP	6	0.2 (0.1)	5	0.2 (0.1)
CH	14	0.3 (0.1)	11	0.5 (0.2)
PB	6	0.2 (0.0)	2	3.0 (1.9)
NV	14	0.2 (0.0)	11	0.3 (0.1)
AR	5	0.2 (0.1)	6	0.7 (0.3)

duration of recording without supplementary oxygen therapy (table I).

Episodic hypoxaemia was seen in both groups. In the meptazinol group 80 % of patients (21/26) had an Sa_{O_2} < 90 % at some time and 23 % (6/26) had an Sa_{O_2} < 85 %. In the morphine group, the corresponding figures were 95 % (22/23) and 47 % (11/23). The mean duration of hypoxic episodes per hour of recording did not differ significantly between groups (table II).

TABLE V. *Number of doses of meptazinol 20 mg or morphine 2 mg (mean (SEM)) demanded by PCA and cyclizine 50 mg given by the ward staff in patients undergoing arthroplasty of the hip.* *P < *0.05 between groups*

	Morphine	Meptazinol
Anti-emetic	0.9 (0.2)	1.5 (0.2)*
Analgesic	11.8 (1.5)	15.0 (2.0)

No episodes of obstructive pause were noted (table III). There was a tendency for more patients in the meptazinol group to have obstructive apnoea and central apnoea, and for those events to occur with greater frequency ($P > 0.05$). There were no other significant differences between the groups.

The meptazinol group recorded significantly greater mean pain scores at the 8-h assessment than the morphine group at the same time ($P < 0.05$). The mean pain scores measured by VRS were similar in both groups (table IV).

The overall patient assessments of analgesic efficacy were similar in the two groups. The meptazinol group recorded a mean VRS of 1.2 (SEM 0.13) and the morphine group recorded a mean VRS of 1.2 (SEM 0.15). There was no significant difference between the two groups in respect of the mean number of demands for analgesic drugs (table V).

The meptazinol group displayed a greater mean LAS for nausea at the 8-h assessment than the morphine group at the same time ($P < 0.05$) (table VI). The meptazinol group experienced also a greater incidence of vomiting and a greater requirement for anti-emetic drugs than the morphine group ($P < 0.05$) (table V). The mean LAS for sedation and dizziness were similar in the two groups at all assessments (table VI).

TABLE IV. *Assessment of pain by 10-cm LAS and five-point VRS (mean (SEM)) in patients receiving morphine or meptazinol at differing times after hip arthroplasty.* n = *Number of patients making an assessment at that time.* *P < *0.05 between groups*

	LAS				VRS			
	Morphine		Meptazinol		Morphine		Meptazinol	
Time (h)	n	Score	n	Score	n	Score	n	Score
2	14	4.3 (0.8)	19	3.9 (0.6)	15	1.7 (0.2)	19	1.4 (0.2)
4	18	4.5 (0.7)	20	4.1 (0.5)	17	1.6 (0.2)	20	1.5 (0.2)
8	11	2.8 (0.9)	12	5.5 (0.7)*	12	1.5 (0.3)	12	1.7 (0.1)
16	10	4.4 (0.8)	12	3.1 (0.7)	10	1.7 (0.3)	12	1.4 (0.2)
24	18	2.7 (0.6)	21	2.9 (0.5)	19	1.1 (0.2)	21	1.2 (0.2)

TABLE VI. *Assessment of sedation, dizziness and nausea by 10-cm LAS (mean (SEM)) at different times in the postoperative period in patients given either morphine or meptazinol.* n = *Number of patients making an assessment at that time point.* *$P < 0.05$ *between groups*

Time (h)	*n*	Sedation	Nausea	Dizziness
Morphine				
2	14	4.0 (0.8)	1.5 (0.6)	1.0 (0.6)
4	18	4.0 (0.7)	1.1 (0.5)	0.7 (0.3)
8	10	3.9 (1.0)	1.9 (1.0)	0.5 (0.3)
16	11	3.6 (0.8)	2.4 (0.9)	2.1 (0.6)
24	19	4.0 (0.7)	1.6 (0.6)	1.4 (0.5)
Meptazinol				
2	18	3.8 (0.6)	2.4 (0.7)	0.5 (0.3)
4	19	3.7 (0.6)	2.2 (0.6)	0.8 (0.4)
8	11	5.3 (0.8)	5.2 (0.8)*	1.9 (0.8)
16	12	3.6 (0.8)	1.4 (0.6)	1.0 (0.6)
24	21	2.6 (0.6)	2.2 (0.7)	1.6 (0.5)

DISCUSSION

Previous studies on the potential of different drugs to affect respiration have relied clinically on intermittent measurements and those made in the laboratory [2–4]. However, the effects of drugs on respiration often extend beyond hypoventilation and mild hypercapnia. The integrity of the upper airway and sleep stage may have profound effects on respiration, particularly on the likelihood of transient events such as central and obstructive apnoea which result in hypoxaemia. Cardiac arrhythmias and pulmonary and systemic hypertension are known to occur commonly during obstructive sleep apnoea and are thought to be related to the accompanying transient hypoxaemia [12]. It follows that the respiratory effects of analgesic drugs are influenced, not only by effects on respiratory drive, but also by effects on upper airway control, sleep and the arousal response to airway obstruction, hypoxia and hypercapnia. Comparisons of drugs should include, therefore, continuous measurement of respiratory variables in addition to usual laboratory investigations.

Patients undergoing arthroplasty of the hip were chosen for this study for several reasons. First, they are elderly and would thus be expected to have a moderate degree of ventilatory disturbance during normal sleep. Ideally, a control recording of ventilation should have been made on a night before surgery, in order to ensure that the groups were comparable. However, the "first night effect" [13] would have necessitated at least two nights of recording and the organizational difficulties were sufficient to make a control recording impracticable. Any patient with symptoms of obstructive sleep apnoea (heavy snoring and daytime sleepiness) was excluded. Second, the patients are required to sleep supine following surgery, thus eliminating confounding effects of a change in sleeping position on the frequency of obstructive apnoea. Third, surgery on the extremities has the least effect on functional residual capacity and thus the effect of the surgical procedure on respiration is minimized.

The administration of equianalgesic doses of two drugs is hindered by their differing side effects and modes of action. PCA was utilized in this study in an attempt to ensure an equal relief of pain. However, the increased incidence of nausea in the patients receiving meptazinol may have resulted in a lesser degree of analgesia than was achieved in those receiving morphine, as it may be assumed that patients using PCA achieve a balance between analgesia and side effects. Both groups of patients reported similar analgesia, suggesting that this factor was not important in this study. Meptazinol has been reported also as causing less sedation than morphine and might thus have less propensity to cause obstructive and central apnoea. Similar degrees of sedation were reported by both groups of patients.

Optimal monitoring of the respiratory effects of drugs should include electroencephalography and electromyography, in order to determine sleep stage, in addition to monitors of ventilation and oxygenation. The necessity for multiple electrodes and the impracticality of undertaking such a study on the open ward led us to reject this degree of monitoring. Experience from our Sleep Laboratory has shown that satisfactory differentiation of respiratory disturbances could be achieved with only two monitors, the oximeter and the RIP [14]. The RIP used (GVT) comprises a single coil of wire arranged around the thorax and abdomen, in contrast with other types which utilize separate coils. The simplicity of the transducer and monitor unit of the GVT was very acceptable to the patients and staff and allowed the study to proceed without continual supervision.

The definition of central hypoventilation may be criticized as arbitary. The signal from the GVT, in common with other inductance plethysmographs, maintains a linear and reasonably constant relationship with thoracic volume change if there is no major change in body position [11]. No calibration of the GVT was used in this study, but the lack of movement in the patients studied makes it reasonable to assume that a consistent reduction in the GVT signal to less than 50% of baseline represents a significant, although unquantified, reduction in tidal volume.

The lesser effect of meptazinol on ventilatory drive in laboratory studies [4] has suggested that it might cause fewer transient ventilatory disturbances than morphine. This supposition was not borne out by this study, where similar effects were seen on oxygenation and ventilation. The reasons for the discrepancy are unclear, although differing effects on upper airway control and the arousal response to hypoxia and hypercapnia may be important.

This study has confirmed the greater propensity of meptazinol to cause nausea and vomiting compared with morphine [4]. There was little difference between the LAS scores for nausea between the groups, illustrating the efficacy of cyclizine in combating nausea induced by meptazinol [15].

We conclude that the effects of meptazinol and morphine on ventilation and oxygenation are similar in the postoperative period when given in approximately equianalgesic doses. This observation contrasts with laboratory findings and confirms the need for continuous monitoring of respiration in the postoperative period as part of the assessment of analgesic drugs and techniques.

ACKNOWLEDGEMENTS

We thank Wyeth Laboratories for practical and financial support.

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Br. J. Anaesth. (1989), **63**, 266–275

TOTAL RESPIRATORY COMPLIANCE DURING ANAESTHESIA IN INFANTS AND YOUNG CHILDREN

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SUMMARY

The multiple occlusion technique was used to study the effects of paralysis on ventilatory mechanics during anaesthesia. Total respiratory compliance (Crs) was measured during spontaneous breathing and following neuromuscular block with controlled ventilation in 23 infants. There was marked variation in response to paralysis: some infants demonstrated no change in Crs between the two states; others had values of Crs which were significantly higher during paralysis with controlled ventilation than during spontaneous breathing. A possible cause of these differences may be the type of controlled ventilation given during paralysis, with tidal volume directly influencing values of Crs obtained. The results of this study suggest that values of Crs obtained during spontaneous breathing and paralysis should not be used interchangeably until further studies have been performed to assess factors influencing Crs during controlled ventilation.

Following induction of anaesthesia, a reduction in both lung volume and compliance has been reported frequently in adults [1–4]. However, despite the fact that it is common practice for young infants to be paralysed and undergo ventilation during anaesthesia, rather than breathe spontaneously, few studies during the first few years of life have been performed to assess the effects of anaesthesia and neuromuscular block on ventilatory mechanics.

During the past few years, a new technique for measuring total respiratory compliance (*C*rs) has been developed and validated [5–9]. This technique, referred to commonly as the multiple occlusion technique, is based on the rationale that, if the infant's airway is occluded briefly during expiration, the Hering–Breuer reflex (HBR) may be induced, resulting in a brief ventilatory pause with relaxation of the muscles of ventilation. Providing that relaxation does occur during occlusion, the pressure which develops at the airway opening reflects the recoil pressure of the lung and chest wall [10]. *C*rs can be calculated by relating the volume occluded in excess of the end-expiratory volume to the corresponding value of relaxed pressure above atmospheric pressure recorded at the airway opening (fig. 1).

Adaptations of the occlusion technique have been applied both to anaesthetized adults and animals [1,11] and to spontaneously breathing infants [12–14] and infants undergoing ventilation [7, 15, 16]. The technique has been shown to be applicable to young children up to 4 years of age [17] and a strong cubic relationship between *C*rs and body length has been demonstrated during the first 1 yr of life in healthy infants [12]. As the occlusion technique avoids the use of oesophageal pressure measurements (which have been shown to be unreliable in preterm, sick, intubated or anaesthetized infants because of uneven distribution of pleural pressure [7, 18, 19]), it should be of particular value when assessing ventilatory mechanics in anaesthetized infants. However, to our knowledge there are no published reports of such measurements.

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Accepted for Publication: December 15, 1988.

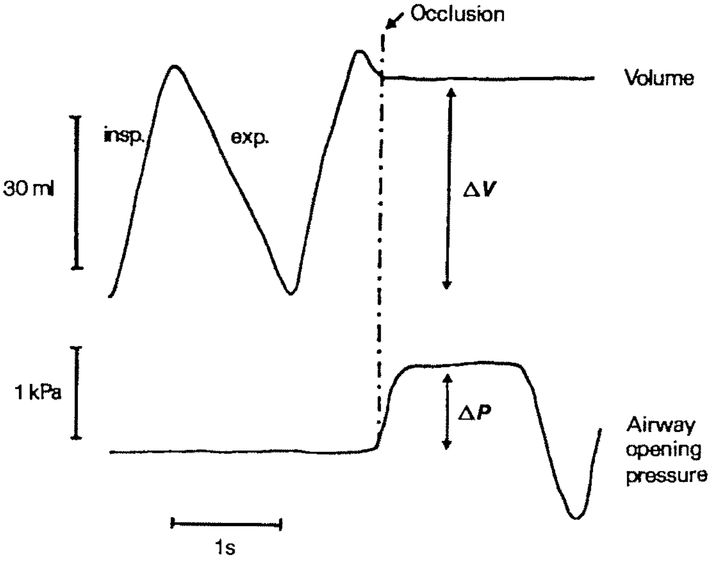

FIG. 1. Tidal volume and pressure changes at the airway opening during airway occlusion in an anaesthetized infant breathing spontaneously.

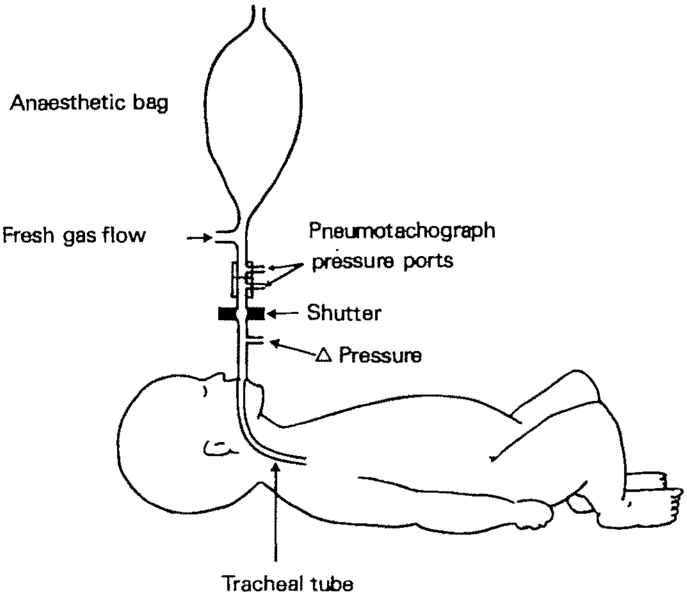

FIG. 2. Patient system used for measurement of *Crs*. The flow signal measured with the pneumotachograph was integrated to give tidal volume.

The aims of this preliminary study were to assess the use of the occlusion technique in anaesthetized children during the first 3 years of life, and to compare values of *Crs* obtained during spontaneous breathing with those measured during controlled ventilation, following administration of a neuromuscular blocking agent.

Approval for this study was given by the hospital Ethics Committee.

METHODS

The apparatus used to measure *Crs* is shown in figure 2. Pressure changes at the airway opening

(Δ *P*ao) were measured at the apparatus end of the tracheal tube using a Validyne MP45 transducer (±5 kPa). Flow was measured with a Fleisch pneumotachograph size 0 in infants younger than 6 months of age and size 1 in older infants. The pneumotachograph was attached to a low pressure range (±0.2 kPa) Validyne transducer and the output was electronically integrated to provide the volume signal (Δ *V*). A bias flow of gas distal to the measuring apparatus (6 litre min^{-1}) was used to permit administration of anaesthetic gases. An anaesthetic bag connected to the distal end of the breathing system enabled manual ventilation to be introduced following administration of the neuromuscular blocker. The deadspace of the system was 7–15 ml, according to the pneumotachograph used, and resistance 0.48 kPa litre^{-1} s at a flow rate of 100 ml s^{-1}.

A manually operated shutter placed promixal to the pneumotachograph was attached to the tracheal tube using a suitable low-deadspace connector. The pneumotachograph was thus not pressurized during occlusions. Recordings of volume, pressure and flow were made in real time onto u.v.-sensitive paper using an SE Labs 3000 UV recorder. Occlusions were timed using a Tektronix 5223 digitizing oscilloscope.

Normal hospital anaesthetic practice was adhered to as closely as possible. Infants weighing less than 10 kg were premedicated with pethidine compound 0.08 ml kg^{-1} (1 ml contains pethidine 25 mg, promethazine 6.25 mg and chlorpromazine 6.25 mg) given 1 h before operation. Those heavier than 10 kg were premedicated with papaveretum 0.4 mg kg^{-1} and hyoscine 0.008 mg kg^{-1}. Anaesthesia was induced with cyclopropane in oxygen ($F\text{I}_{\text{O}_2}$ = 0.5) until consciousness was lost, then maintained with nitrous oxide and 1–1.5% halothane in oxygen ($F\text{I}_{\text{O}_2}$ = 0.5). Suxamethonium 1 mg kg^{-1} was given to facilitate tracheal intubation.

When tidal breathing had recommenced with a regular tidal volume and rate, measurement of *C*rs was made during spontaneous breathing using an adaptation of the multiple occlusion technique [6, 12].

When the infant was breathing quietly through the apparatus, 15–25 expiratory occlusions were performed at different lung volumes within the tidal range. At least 10 breaths were allowed between each occlusion to enable stabilization of the end-expiratory volume (EEV). Providing that a pressure plateau of at least 0.2 s was achieved, indicating relaxation of the ventilatory muscles, the volume above EEV during each occlusion (Δ *V*) was related to the corresponding pressure change at the airway opening (Δ *P*ao).

A non-depolarizing neuromuscular blocker was given to paralyse the child before surgery. During the subsequent controlled ventilation, which was performed manually, brief airway occlusions were performed at different lung volumes during passive deflation. Following release of the occlusion, the expired volume was related to the pressure plateau which had developed at the airway opening during the occlusion (fig. 3). At

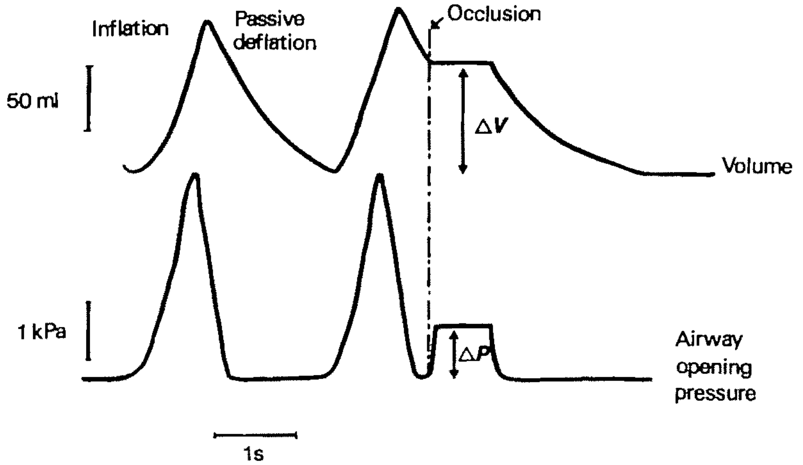

FIG. 3. Tidal volume and pressure changes at the airway opening during airway occlusion in a paralysed, anaesthetized infant undergoing manual ventilation.

TABLE I. *Individual details and results. Cs = Respiratory compliance during spontaneous breathing; Cp = respiratory compliance during paralysis; CI = confidence interval for ratio.* P *value for paired* t *test between states. Compliance values rounded up to nearest whole number. *Possibly abnormal cardiopulmonary status (see text)*

Patient No.	Weight (kg)	Length (cm)	*Cs* (ml kPa^{-1})	*Cp* (ml kPa^{-1})	*Cp*:*Cs*	95% CI for *Cp*:*Cs*	*P*
29	5.1	60.0	33	28	0.87	0.69–1.05	0.156
44*	6.6	63.5	39	35	0.89	0.78–1.00	0.051
45*	10.1	81.0	115	102	0.89	0.76–1.02	0.102
13	12.7	88.0	136	122	0.89	0.44–1.34	0.619
57	10.0	84.0	68	61	0.90	0.67–1.13	0.366
69	9.4	74.0	74	75	1.02	0.78–1.27	0.826
36*	10.1	83.0	129	134	1.03	0.94–1.12	0.463
21	9.7	66.5	88	93	1.05	0.89–1.21	0.464
31*	6.7	73.0	102	107	1.05	0.89–1.20	0.556
2	10.6	82.0	95	102	1.08	0.93–1.23	0.275
49	13.0	86.5	107	120	1.13	0.95–1.31	0.156
60*	11.8	90.5	127	146	1.15	0.94–1.36	0.148
14	12.1	86.5	129	148	1.15	1.03–1.26	0.014
43	9.2	77.5	81	94	1.16	0.86–1.46	0.269
59*	11.3	77.5	47	54	1.16	0.49–1.82	0.606
18*	10.4	77.0	81	95	1.17	1.05–1.29	0.009
25*	5.6	65.0	41	48	1.17	1.04–1.30	0.015
39	7.0	66.5	36	44	1.21	1.08–1.34	0.015
20	12.4	86.0	78	110	1.41	1.13–1.69	0.007
74*	7.5	66.0	40	58	1.47	1.26–1.68	0.001
65*	10.8	77.0	61	93	1.52	1.36–1.68	0.000
73	5.3	59.5	47	83	1.76	1.49–2.03	0.000
58	7.1	69.0	33	58	1.77	1.38–2.17	0.002

least 10 such occlusions were obtained with the infant undergoing manual ventilation for a minimum of five breaths between each occlusion.

No attempt was made to control the pattern of ventilation given by the anaesthetist during paralysis except to ensure that, following the release of each airway occlusion, adequate time was allowed during the subsequent passive expiration for the lung to reach its relaxed functional residual capacity before the next re-inflation. This was determined by observing the flow and pressure traces on the oscilloscope. All studies were completed within 20 min of the induction of anaesthesia.

Analysis of results

Care was taken to avoid potential errors in this technique by applying to data analysis strict criteria as established in this department [6], including rejection of data if there was evidence of active expiration or leaks during the occlusion. In order to avoid potential errors in the presence of dynamic lung elevation [20, 21], *C*rs was calculated as the slope of the volume–pressure data by least squares regression analysis. This took into account any intercept that might occur on extrapolation of the *V–P* data, thereby preventing any underestimation of *C*rs [5]. A squared correlation coefficient (R^2) between 0.89 and 0.999 was found in infants in whom technically satisfactory data were obtained.

Subjects

Attempts to measure *C*rs during paralysis and spontaneous breathing were made following tracheal intubation in 74 anaesthetized infants and young children during the first 3 years of life. Although a satisfactory measurement of *C*rs was obtained during one or other of the states in 66 of the infants, reliable measurements during both spontaneous and controlled ventilation using Stocks' criteria [6] could be obtained in only 23 of these subjects.

Details of the 23 infants and young children (ages 1 month to 2 years 7 months) in whom a reliable comparison of *C*rs during spontaneous breathing and controlled ventilation could be made are included in table I. Of these children, 13 were known to have normal cardiopulmonary status, whereas the others had some form of neuromuscular, skeletal or renal disease which could potentially influence lung function.

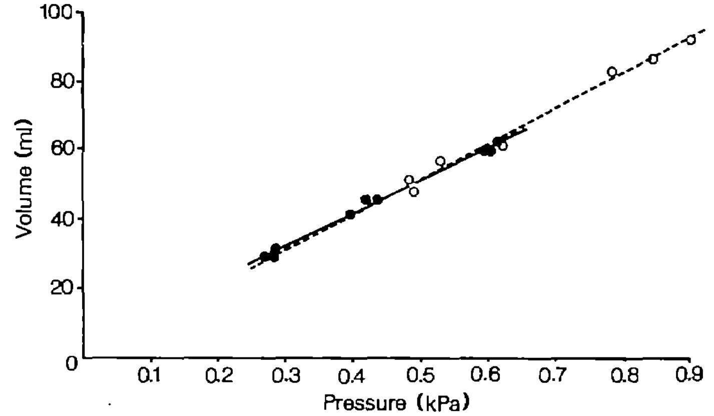

FIG. 4. Volume–pressure plots from infant No. 2. ●——● = Spontaneous breathing (*Cs* 95 ml kPa^{-1}); ○——○ = paralysed (*Cp* 102 ml kPa^{-1})—no significant change.

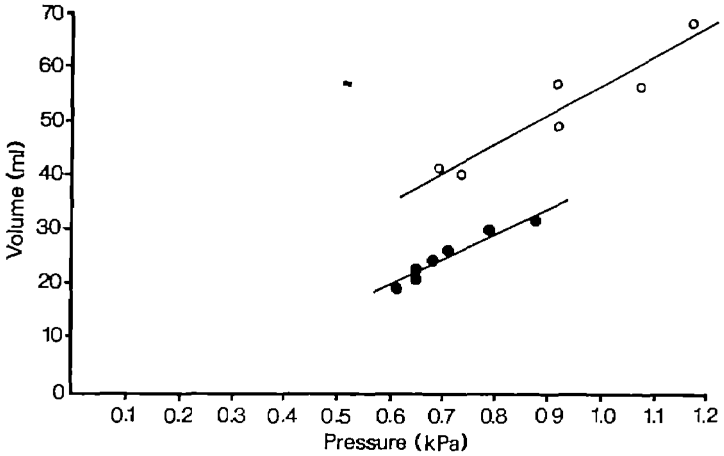

FIG. 5. Volume–pressure plots from infant No. 60. ● = Spontaneous breathing (*Cs* 47 ml kPa^{-1}); ○ = paralysed (*Cp* 54 ml kPa^{-1})—possible change.

Children undergoing thoracic surgery were excluded from the study.

RESULTS

The variability of absolute values of *C*rs obtained from individual infants (table I) largely reflected the fact that there is a rapid increase in *C*rs during the first 2 years of life [12, 17]. In order to standardize the effects of growth and enable meaningful comparisons to be made between infants, results were expressed as the ratio of *C*rs obtained during paralysis to that recorded during spontaneous breathing (*C*p:*C*s) in each infant. This ranged from 0.87 to 1.77 (table I). The 95% confidence interval for this ratio was calculated also for each infant. The width of such an interval reflects the scatter of volume data around the regression lines, the number of satisfactory occlusions obtained in each child and the pressure range over which they were collected [22, 23]: the wider the confidence interval, the larger the change that must occur between any two states before the difference is statistically significant.

In some infants, values of *C*rs during paralysis were similar to those obtained during spontaneous breathing, the narrow 95% confidence intervals of the *C*p:*C*s ratios encompassing unity (e.g. infants Nos 2, 36 and 31). In such infants, the small difference between states was not significant

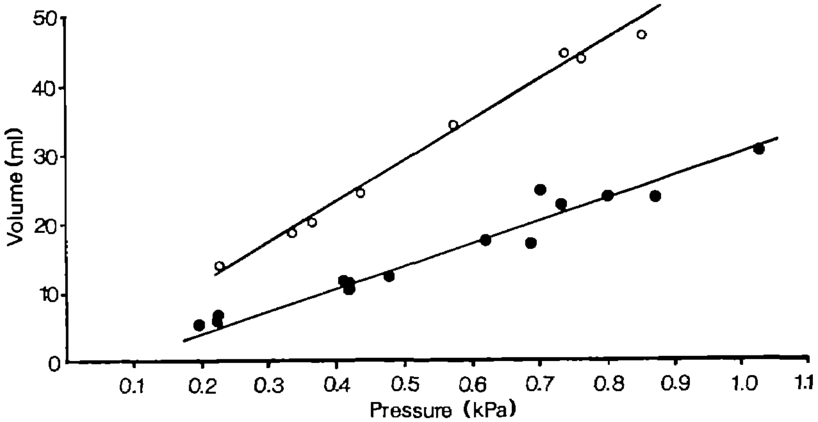

FIG. 6. Volume–pressure plots from infant No. 58. ● = Spontaneous breathing (*Cs* 33 ml kPa^{-1}); ○ = paralysed (*Cp* 58 ml kPa^{-1})—significant change.

and was probably too small to be of clinical or physiological importance. Figure 4 illustrates the results from infant No. 2, in whom values for *Crs* were virtually the same in both states.

The calculated values of *Crs* during spontaneous breathing and paralysis were similar in many of the infants with 95 % confidence intervals for the *Cp*:*Cs* ratios including unity and high *P* values, indicating that these differences were not significant. However, in some of these infants (e.g. infants Nos 13, 60 and 59) wide confidence intervals occurred indicating that, although a marked difference between the two states may have been present, there was insufficient evidence to judge conclusively. Figure 5 illustrates the results from infant No. 60. By contrast, other infants (e.g. infants Nos 58, 73 and 65) demonstrated an increase in *Crs*, with the whole of the 95 % confidence interval for the *Cp* : *Cs* ratio being greater than unity. Even in infants with wider confidence intervals (e.g. infants Nos 20 and 58), the differences were so large that these increases were significant. Results from infant No. 58 are shown in figure 6. There were no occasions on which a significant decrease in *Crs* was observed during paralysis.

DISCUSSION

This study has demonstrated that the multiple occlusion technique may be applied to anaesthetized infants and young children during both spontaneous breathing and following administration of a neuromuscular blocking drug.

Measurements of *Crs* in at least one state were obtained in 66 of the 74 infants studied, despite adherence to the strict criteria for quality control established previously [6] and the constraints of studying anaesthetized infants before operation. These criteria included absence of leak on inspection of the volume and pressure traces, and a minimum of five pressure plateaux during occlusions in which there was no evidence of active expiration and which encompassed a pressure range of at least 0.3 kPa.

The major reason for failing to obtain satisfactory results during spontaneous breathing was persistent failure to relax during airway occlusion. During controlled ventilation, failures resulted predominantly from inadvertent application of positive end expiratory pressure or a leak around the tracheal tube which could not be controlled temporarily by gentle cricoid pressure. Lack of time was another major reason for failing to obtain both sets of results as every effort was made not to interfere with the normal operating schedule. A large number of the early failures were a result of developmental problems with the shutter mechanism.

The significance of our findings depends largely on the assumption that the same variable—namely the compliance of the passive respiratory system—was being measured during both spontaneous breathing and controlled ventilation. Following neuromuscular block, passive conditions could be ensured. However, the accuracy of the measurement during spontaneous breathing rests largely on the assumption that the change in tracheal pressure during airway occlusion represents passive elastic recoil of the respiratory system.

It is known that, in adults, anaesthesia may induce expiratory muscle activity [24]. Kaul, Heath and Nunn [25] measured EMG activity in the external oblique muscle and found that expiratory muscle activity developed within 29 min of inducing anaesthesia in 20 of the 22 adults studied. This activity decreased but was not abolished during inhalation of increasing concentrations of halothane.

All our infants received 1–1.5% halothane during anaesthesia, but the presence of active expiration was evident on many occasions, from the increase in tracheal pressure during airway occlusions. In some infants, this pattern was so persistent that *C*rs could not be calculated during spontaneous breathing. However, in the infants reported in this study, satisfactory pressure plateaux lasting at least 0.2 s, and at times as long as 1 s, were obtained sufficiently frequently to enable accurate calculation of *C*rs.

Although the vagally mediated Hering–Breuer reflex is thought to be weak or absent during normal tidal breathing in adults, it has been shown to persist in children up to 4 years of age [17]. However, without direct measurements of gastric pressure or EMG [26], it is not possible to exclude active expiration as a contributory factor to the differences observed in some infants. Unfortunately, accurate recordings of EMG from surface electrodes are difficult to obtain and would have significantly prolonged the duration of this study.

Several studies have been performed to validate the occlusion technique, using the presence of a pressure plateau to reflect muscle relaxation. Thomson (9) found no significant difference between *C*rs by the occlusion technique during spontaneous ventilation and total compliance from volume–pressure data following induction of apnoea in 12 infants. The same authors compared measurements of *C*rs by the occlusion technique with dynamic lung compliance in low birth weight infants and found that in infants in whom it was possible to obtain a satisfactory oesophageal pressure recording, *C*rs by the occlusion technique was always within 25% of dynamic lung compliance (*C*dyn,L) [7]. As *C*rs includes the compliance of the chest wall, one would not expect values of *C*dyn,L to agree perfectly with *C*rs. However, in a study on newborn lambs [8], static compliance of the chest wall was measured directly so that it could be subtracted from *C*rs to obtain a meaningful comparison with *C*dyn,L. The mean static lung compliance of 2.38 (SD 0.54) ml cm H_2O^{-1} by the occlusion technique was not significantly different from dynamic lung compliance (measured from oesophageal pressure recordings) which was 2.58 (0.59) ml cm H_2O^{-1} in these healthy lambs breathing room air.

Various methods of differing complexity have been applied to assess compliance in anaesthetized infants [27–30], but not all have taken into account the compressible volume of the ventilator system or detailed how potential errors (such as leaks around the tracheal tube) have been recognized. The considerable variation in published results has been ascribed to differences in methodology, influence of volume history or the pressures utilized. The influence of volume history is unlikely to have been a major determinant of the variable response to paralysis seen in this study, as all infants received three inflations to 2.5 kPa before measuring *C*rs during the controlled ventilation.

In the presence of a long time constant and short expiratory time, there may be insufficient time for complete expiration to occur during spontaneous breathing, resulting in dynamic increase in lung volume [20, 21]. As *C*rs was calculated by least squares regression analysis of the *V–P* data in this study, the presence of this phenomenon would have been evident from a negative intercept on the volume axis. However, all the infants reported in this study had marginal and insignificant intercepts (< 1 ml kg^{-1}) during spontaneous breathing, which would have been insufficient to contribute to any changes noted following paralysis.

Similarly, errors could occur during controlled ventilation if insufficient time were allowed for complete emptying of the lung following release of the occlusion [31]. However, we took care to avoid this problem by ensuring that zero flow and volume were achieved during passive expiration before the subsequent inflation. It appears likely, therefore, that the changes observed in some infants were not caused by technical errors but reflected a real change in the volume–pressure characteristics of the lungs during controlled ventilation.

Had we subjected the results of the 23 successful comparisons to a paired *t* test as is commonly the case in such studies, we should have demonstrated an increase in *C*rs during paralysis, that was significant at the 1% level.

However, this would have masked the very wide individual response that occurred. By determining the 95% confidence intervals for each child's results, the individual changes could be interpreted more readily. The most striking element of these results is the very wide variation in individual response to paralysis.

The confidence intervals for the individual *Cp*:*Cs* ratios were related directly to the scatter of the *V*/*P* points, the pressure range over which they were successfully collected, and the number of occlusions. The wider the confidence interval, the greater the difference between two measurements before statistical significance was reached. Therefore, in some infants (e.g. infants Nos 21 and 31) any real difference present could not be proven. However, in some infants there was conclusive evidence that there was no clinically or statistically significant difference between values of *C*rs obtained during spontaneous breathing and paralysis. In other infants there was a signficant increase in *C*rs of at least 15% on paralysis, with the entire confidence interval for the *Cp*:*Cs* ratio exceeding unity.

In this laboratory, repeat measurements of *C*rs taken over time have been found to have values within 10% of each other (mean difference 5.1% in 13 infants). A change of 15% falls outside the variation between measurements and may also be of clinical importance.

To our knowledge, no similar comparative studies have been performed in infants and young children. Studies in adults have suggested that there is no significant difference between values of *C*rs obtained during spontaneous breathing and paralysis in anaesthetized subjects [3]. However, the power of some of these studies may have been too small to detect real differences because of the small number of subjects studied and the large scatter of results [1].

Results from two infants, who were excluded from the study because of the unusual marked scatter of their volume–pressure data (fig. 7) during paralysis (which prevented an accurate

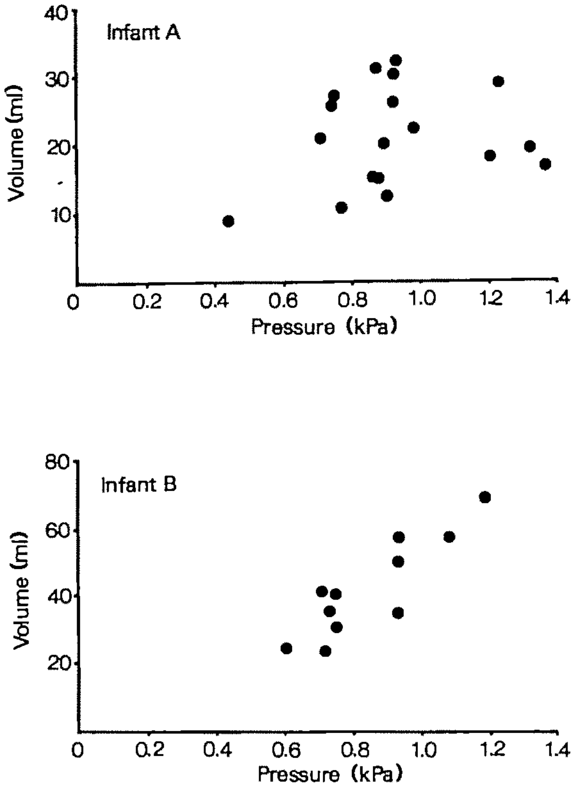

FIG. 7. Volume–pressure plots during paralysis in infant A (age 1 month, weight 4.18 kg) and infant B (18 months, 11.3 kg).

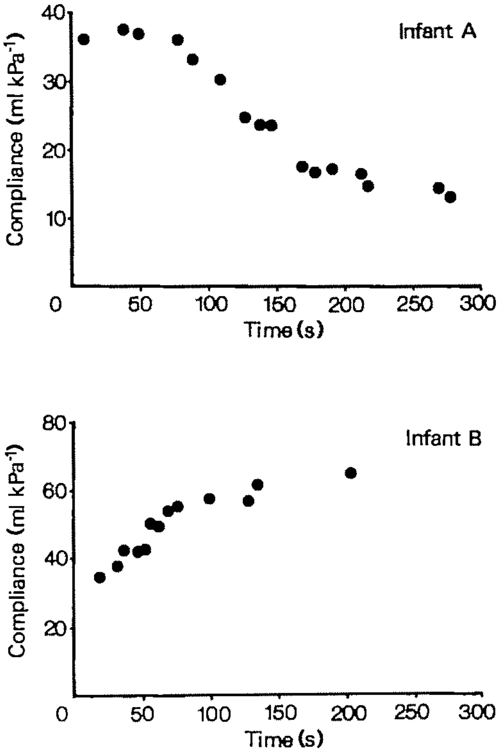

FIG. 8. Compliance during paralysis (calculated as $\Delta V/\Delta P$ from individual occlusions) plotted against time, in infants A and B.

assessment of *C*rs by regression analysis), provided an important clue as to the possible cause for the observed inter-individual variability of the results. On further examination of the time based records from these infants, *C*rs was found to be changing progressively with time (fig. 8). Infant A showed a decrease with time and infant B an increase. The most likely explanation for these changes appears to be the pattern of manual ventilation administered during paralysis as evident from the continuous recording of tidal volume. In infant A, ventilation was very gentle following onset of paralysis, at a rate of 15 b.p.m., with peak pressures of 2–2.5 kPa. Initially, the measured *C*rs was similar to that during spontaneous breathing. Within 4 min it had halved. In contrast, infant B underwent ventilation at 60 b.p.m. with peak pressures of 2.5–3 kPa.

Lung volume is known to decrease during halothane anaesthesia, probably because of compression atelectasis [4, 32–34]. Breathing at this lower lung volume may occur along the stiffer portion of the S-shaped volume–pressure curve, reflected in lower values of *C*rs. Infant A may have undergone further atelectasis because of the low rate and volume of ventilation, achieving lung compliances progressively lower on the curve with time.

With larger tidal volumes, progressive reinflation of atelectatic areas may occur, such that breathing occurs on the steeper portion of the curve with a resultant increase in *C*rs. Rate of ventilation may have contributed also to this effect, the more rapid rate used for infant B facilitating progressive increase in lung volume by preventing complete emptying between inflations before the occlusion.

The inter-individual variability in response to paralysis seen in this study may reflect the fact that some infants underwent more vigorous ventilation than others following neuromuscular block. Until this hypothesis is tested, values of *C*rs obtained during spontaneous breathing and paralysis should not be used interchangeably.

ACKNOWLEDGEMENT

This study was supported by the British Heart Foundation.

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Br. J. Anaesth. (1989), **63**, 276–282

EFFECT OF PEROPERATIVE NORMOTHERMIA ON POSTOPERATIVE PROTEIN METABOLISM IN ELDERLY PATIENTS UNDERGOING HIP ARTHROPLASTY

F. CARLI, P. W. EMERY AND C. A. J. FREEMANTLE

Surgical injury is followed by metabolic alterations secondary to tissue damage and neuroendocrine changes. Much of the protein loss occurs in skeletal muscle, as demonstrated by increased release of amino acids from muscle [1]. The accelerated release of amino acids is associated with increased loss of nitrogen and body cell mass.

In a previous study [2] protein breakdown was attenuated by conservation of body heat during major abdominal surgery, resulting in decreased urinary excretion of 3-methylhistidine (3-MeH) and urea nitrogen. However, the validity of 3-MeH excretion as an index of muscle breakdown has been questioned by Rennie and Millward [3], who suggested that large quantities of this amino acid come from breakdown of visceral protein in organs such as gut.

During abdominal surgery, the contribution of muscle breakdown to the excretion of 3-MeH might play a minor role compared with the gut, which is directly involved in such surgery. We decided, therefore, to study 3-MeH excretion using a surgical model associated with muscle damage but not gut involvement. In addition, we investigated the effect of peroperative normothermia on amino acid concentrations in plasma and muscle and on total body potassium, an index of body cell mass.

SUMMARY

We have examined in elderly patients the effect of maintenance of normothermia during hip surgery on postoperative protein metabolism. In one group of six patients (warmed group) heat loss was minimized during surgery and in the recovery period by warming fresh gases, i.v. fluids and wrapping the exposed parts of the body with a warming blanket. In a second group of six patients (cold group), routine care was provided. General anaesthesia consisted of thiopentone, tubocurarine and halothane in both groups. Urinary excretion of urea nitrogen and 3-methylhistidine (3-MeH) after surgery was significantly lower in the warmed group compared with the cold group ($P < 0.05$*). There was little effect of normothermia on amino acid concentrations in plasma after surgery. Muscle glutamine concentration 4 days after surgery decreased by 50% in the cold group and 18% in the warmed group. Total body potassium (TBK), measured as an index of body cell mass, decreased significantly after surgery in both groups. However, 7 days after surgery the reduction in TBK in the cold group remained significantly lower than that of the warmed group (*$P < 0.05$*). Maintenance of normothermia during hip surgery appeared to attenuate, but not eliminate, protein breakdown and nitrogen loss after surgery.*

PATIENTS AND METHODS

Twelve elderly patients undergoing elective hip arthroplasty for osteoarthritis gave informed consent to participate in this study, which was approved by the local Ethics Committee. Patients who were grossly obese or malnourished or who had endocrine abnormalities were not included.

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Accepted for Publication: February 20, 1989.
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On the day before surgery, skinfold thicknesses and mid-arm circumference were measured to calculate the ratio of fat to body weight. The duration of preoperative starvation was recorded also.

Premedication comprised papaveretum 15–20 mg and hyoscine 0.2 mg i.m. 60 min before surgery. General anaesthesia was induced with thiopentone and neuromuscular block achieved with tubocurarine. The lungs were ventilated with a mixture of 70 % nitrous oxide in oxygen supplemented by halothane. Normocapnia was ensured by monitoring the end-tidal concentration of carbon dioxide. The patients studied were allocated randomly to two groups (cold and warmed) of six patients each. The cold group served as a control, and no precautions were taken during anaesthesia and surgery to maintain normothermia. In contrast, in the warmed group, efforts were made to minimize heat loss during surgery. This was achieved by warming i.v. fluids to 37 °C using a blood warmer and delivering inspired gases by means of a cascade humidifier (Bennett) set to deliver gases at 36 °C at mouth level. All exposed parts of the body except the operated site were covered with heated blankets at 37 °C. At the end of surgery, a metallized plastic sheet was placed over the patient to minimize heat loss during recovery.

During surgery all patients received an i.v. infusion of normal saline 4 ml kg^{-1} h^{-1}. Dextran 70 in saline was administered when blood loss exceeded 20 % of the patient's circulating volume. After operation, i.v. fluids consisted of a mixture of 4 % dextrose in 0.18 % normal saline at a rate of 40 ml kg^{-1} day^{-1} for 2 days, followed by oral diet.

Before induction of anaesthesia, a thermocouple probe was inserted under direct vision in the aural canal and secured with cotton wool to avoid draughts. Skin surface temperature probes were applied to the chest, mid-arm, mid-thigh and calf and mean skin temperature was calculated. All the probes and the thermometer had been calibrated previously and were accurate to 0.1 °C over the temperature range studied. The measurements were taken before induction of anaesthesia and at the end of surgery. Mean skin temperature was calculated using the four-point formula proposed by Ramanathan [4]: mean skin temperature (°C) $= 0.3$ (t° chest $+ t^\circ$ arm) $+ 0.2$ (t° thigh $+ t^\circ$ calf). Ambient temperature and relative humidity in the operating theatre were kept at 21 °C and 55 %, respectively, during the study.

All patients were maintained on a meat- and fish-free diet for a period of 4 days before surgery and for 4 days afterwards. Oral diet, based on 40–60 g of proteins and approximately 1000 calories per day was resumed on the 3rd day after operation. Surgery was performed by the same surgeon during the morning hours.

Venous blood samples were collected after a 12-h overnight fast on the day of surgery, and on the 2nd and 4th days after surgery for measurement of plasma concentrations of amino acids. Urine was collected for 24 h before and for 4 consecutive days after operation for measurements of urinary concentrations of urea nitrogen, creatinine and 3-MeH.

Percutaneous needle muscle biopsies were taken after a 12-h overnight fast from the lateral portion of the quadriceps femoris muscle, approximately 12–20 cm above the knee [5]. These were performed on the non-operated thigh after induction of general anaesthesia before surgery, and on the 4th day after operation under local anaesthesia. In addition, a small sample of the quadriceps femoris muscle on the operated side was taken by the surgeon immediately after skin incision. The wet biopsy material was dissected carefully to remove visible fat and connective tissue and frozen in liquid nitrogen. The samples were used for measurement of free amino acids.

Biochemical assay methods

Urea nitrogen and creatinine were determined by the SMA automated procedure.

Urinary 3-MeH was measured by high pressure liquid chromatography (HPLC) using a modification of the method of Jones, Shorley and Hitchcock [6]. Urine was diluted 1:10 with water, and 100 µl was mixed with 400 µl of borate buffer (0.1 mol $litre^{-1}$, pH 9) and 500 µl of fluorescamine (1.6 ng ml^{-1} in acetonitrile). After the mixture had stood for 5 min, 500 µl of HCl 2 mol $litre^{-1}$ was added and the mixture heated to 80 °C for 1 h. After cooling, 20 µl was injected onto a reversed phase column (Ultrasphere ODS from Beckman, Bucks) and eluted isocratically with a mixture of 52 % acetate buffer (sodium acetate 1 g and glacial acetic acid 2.5 ml $litre^{-1}$) and 48 % methanol at a flow rate of 1 ml min^{-1}.

The detector was a Gilson Spectra Glo fluorimeter with excitation below 390 nm and emission above 460 nm. 3-MeH concentration was calculated from peak areas by comparison with external standards run with each batch of urine samples.

Plasma samples were deproteinized by the addition of an equal volume of 8% sulphosalicylic acid. After centrifugation the supernatants were analysed for amino acids by HPLC as described previously [7].

Muscle samples were freeze-dried then homogenized in a small volume (30 µl mg^{-1}, dry weight) of 8% sulphosalicylic acid. After centrifugation, the protein-free supernatant was analysed for amino acids by HPLC as above. The method is based on that described first by Turnell and Cooper [8]; in our laboratory we have found its accuracy and precision to be similar to that reported by those authors. Thus for intracellular amino acids present at low concentrations (approximately 10 µmol litre^{-1} in the final sample) the within assay coefficient of variation was 5–10%; for amino acids present at higher concentrations (up to 1000 µmol litre^{-1} in the final sample) the within assay coefficient of variation was 1–5%.

The results were expressed as µmol g^{-1}, wet weight (instead of dry weight), for ease of comparison with previous data [9].

Total body potassium (TBK) was measured non-invasively by use of a whole body counter with a precision of 2% and an accuracy of 4%. The method relies on the measurement of gamma emission from naturally radioactive potassium (potassium-40) present in the body as 0.012% of the stable isotopes of potassium (potassium-38 and potassium-41). As 98% of potassium is located in the cells of the body cell mass, this measurement represents an index of the lean tissue mass. Age, sex, preoperative body weight and height of each patient were recorded, and a predicted value calculated according to formulae proposed by Boddy [10]. The degree of preoperative depletion was calculated from the ratio between the predicted and measured preoperative values, and the metabolic response to surgery was obtained from the difference between the preoperative and postoperative measured TBK concentrations. TBK was measured before surgery and 4 and 7 days after surgery.

Data are presented as mean and standard deviation. Comparison of data within a group was made by applying Student's paired *t* test. Comparisons between groups were performed by the two-sample *t* test for unpaired data.

RESULTS

TABLE I. *Physical characteristics of the two groups, clinical data and body temperature changes during surgery (mean (SD)). ** Statistically significant difference between values for cold and warmed groups* ($P < 0.01$)

	Cold ($n = 6$)		Warmed ($n = 6$)
Age (yr)	71 (6)		67 (8)
Sex M:F	4:2		3:3
Body weight (kg)	71.4 (13.8)		68.3 (19)
Body height (m)	1.68 (11.2)		1.59 (7.9)
Body fat (%)	33.4 (4.2)		32.9 (2.8)
Preoperative starvation time (h)	14 (2)		12 (2)
Duration of surgery (min)	168 (41)		157 (30)
Blood loss (ml)	1368 (400)		1346 (520)
Change in aural canal temperature (°C)	−1.3 (0.3)	**	+0.2 (0.2)
Change in mean skin temperature (°C)	−1.4 (0.2)	**	+0.4 (0.2)

The groups were comparable except for core and mean skin temperatures, which decreased significantly in the cold group by 1.3 and 1.4 °C, respectively, at the end of surgery. In the warmed group, body temperature was maintained at preoperative values during surgery and in the immediate postoperative period. Patients in the cold group rewarmed to the preoperative body temperature during the first 4 h after operation (core of 36.6 °C), while the warmed group maintained core at 36.8 °C (table I).

Urea nitrogen and 3-MEH excretion

Preoperative values of urinary urea nitrogen were similar for both groups. Cumulative concentration of urea nitrogen over 4 days after operation was significantly greater in the cold group compared with that of the warmed group: $1240 + 558$ mmol day^{-1} for the cold group and $728 + 254$ mmol day^{-1} for the warmed group ($P < 0.05$). Urinary excretion of 3-MeH, expressed as the ratio of 3-MeH over creatinine, showed a significantly greater increase 4 days after surgery in the cold group compared with the warmed group (fig. 1).

Plasma and muscle amino acids

Changes in amino acid concentration in plasma and muscle after surgery are shown in figures 2 and 3. Plasma and muscle concentrations of branched chain amino acids increased in both groups. There was no difference in the magnitude of this response between the two groups. The concentration of glutamine in muscles decreased

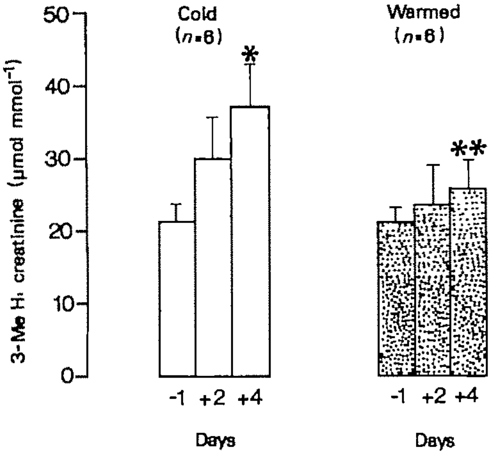

FIG. 1. Urinary excretion of 3-MeH before and 2 and 4 days after surgery in the cold and warmed groups. *Significant difference between values for preoperative and postoperative periods in the cold group ($P < 0.05$); **Significant difference between postoperative values for cold and warmed groups ($P < 0.01$).

in both groups after surgery; however, the decrease in the cold group was more than 50 %, compared with 18 % in the warmed group (fig. 3). The difference between the two groups was not significant because of the small number of patients from whom muscle biopsies were taken (four in each group). Before operation the concentration of glutamine in the muscle of the side to be operated on was significantly lower than that of the unaffected side (10.1 (2.2) v. 13.4 (2.3) μmol g^{-1} (wet weight) $n = 8$, $P < 0.05$ by paired sample t test). There were no other significant differences in muscle amino acid concentrations between the two legs before operation. The preoperative samples had a water content of approximately 71 %, and postoperative samples one of 75 %.

Total body potassium (*TBK*)

No preoperative depletion, calculated as a percentage ratio of measured over predicted value of TBK was observed in either group of patients

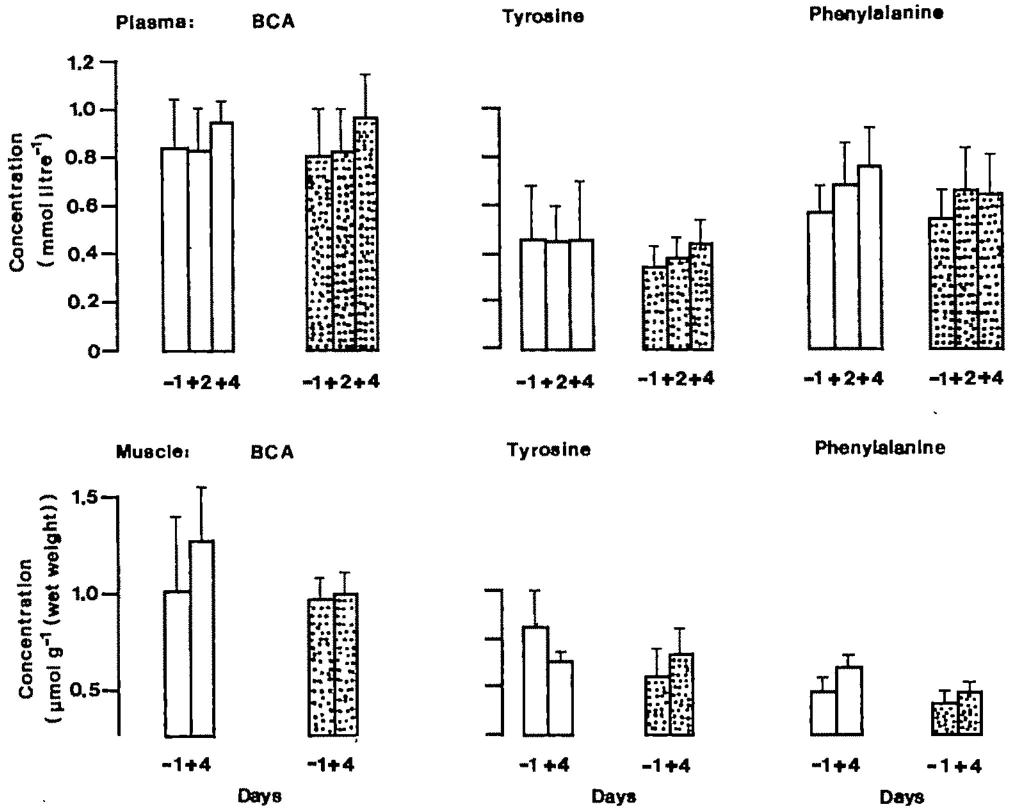

FIG. 2. Preoperative and postoperative plasma and muscle concentrations of branched chain amino acids (BCA) and aromatic amino acids (phenylalanine and tyrosine) in cold group (open columns) and warmed groups (stippled columns).

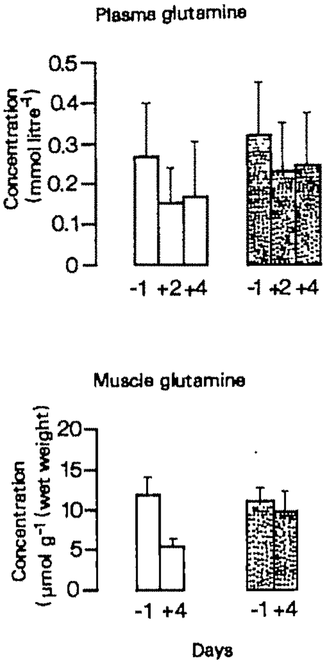

FIG. 3. Preoperative and postoperative plasma and muscle concentrations of glutamine in the cold group (open columns) and warmed group (stippled columns).

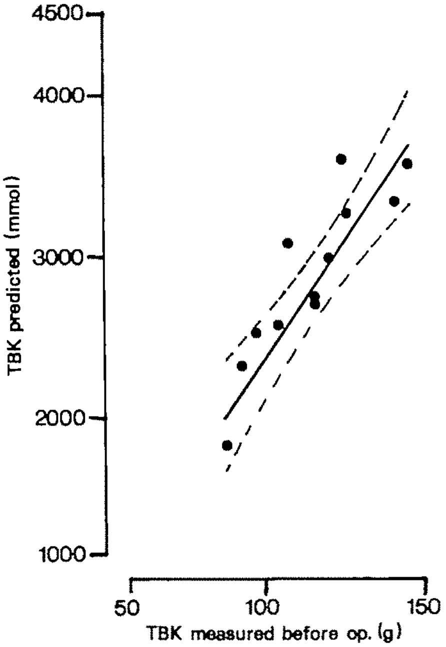

FIG. 4. Correlation between preoperative predicted and measured total body potassium concentration (TBK) in both groups studied, with 95% confidence limits.

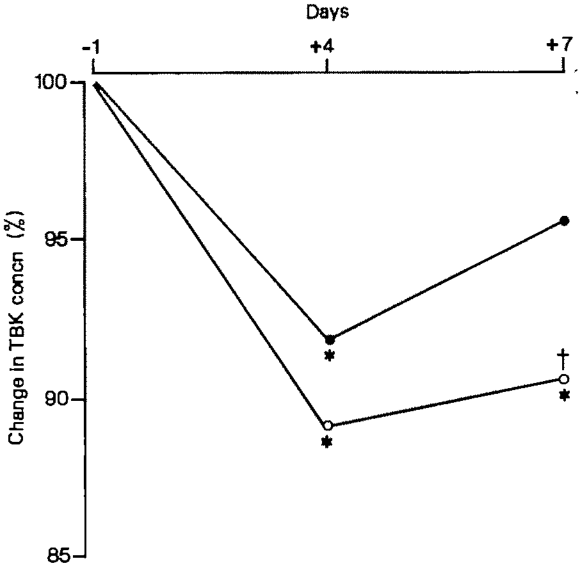

FIG. 5. TBK concentration changes during the postoperative period represented as percentage changes from the preoperative values in the cold group (○) and warmed groups (●). Significant differences ($P < 0.05$): † between postoperative values for cold and warmed groups; * compared with day −1.

studied (fig. 4). The mean (SD) values for the cold and warmed groups were 0.97 (0.12) and 1.03 (0.15), respectively. The postoperative reduction in TBK, represented as percentage change from preoperative value, was similar in both groups 4 days after surgery. However, 7 days after surgery, the change in cell body mass in the warmed group was significantly smaller than that of the cold group ($P < 0.05$) (fig. 5).

DISCUSSION

Maintenance of normothermia during hip surgery resulted in a significant decrease in postoperative urinary excretion of urea nitrogen and 3-MeH. These data are in agreement with two previous studies on protein metabolism in patients undergoing major abdominal surgery [2, 11].

The changes in amino acid concentrations in plasma and muscle were not significantly different between the two groups. The pattern of amino acids is known to be influenced by numerous factors, including age [12], sex distribution [13], dietary intake and physical activity [14]. As far as physical activity is concerned, patients on a waiting list for hip arthroplasty become inactive and some muscle wasting may occur. This may explain the significantly different amino acid concentrations observed in the quadriceps of the operated side compared with the contralateral side. Although physical inactivity does not seem to change the composition of amino acids in muscle in the short term, disuse of specific muscles does lead to atrophy which is characterized by changes in intracellular amino acid patterns, including decreased glutamine concentration [14], as observed here. This finding is of interest because of possible therapeutic implications. Maintaining mobility before surgery may be expected to improve the rate of recovery after the operation.

No attempt was made to control dietary intake before operation, except for a meat- and fish-free diet. However, judging from the anthropometric characteristics of the subjects in both groups (height, weight, body fat %) and preoperative TBK concentration and urea nitrogen excretion, there was no difference between the two groups. Hypocaloric intake was ensured for the first 2 days after operation, followed on days 3 and 4 by a vegetarian diet which included a moderate amount of proteins. The alterations in plasma and muscle amino acids reported here are in good agreement with findings in patients who received different types of nutrition during the postoperative period [15]. This suggests that the metabolic milieu observed in the injury state causes changes in muscles which nutrition can affect only in minor ways. Concentrations of branched chain amino acids increased after surgery, presumably because of the net breakdown of muscle protein.

A greater decrease (50%) in muscle glutamine concentration was observed in the cold group than in the warmed group. This difference was not significant; however, the change observed was of some interest because it was consistent in the small number of patients studied. It has been suggested that the size of the intracellular free pool of glutamine may be important in determining acute changes in protein mass by controlling the rate of protein synthesis in muscle [16, 17]. Thus the attenuation of the loss of glutamine from muscle in the warmed group is further evidence that peroperative warming may ameliorate postoperative loss of muscle protein.

TBK was measured in these patients before and after surgery and used as an absolute index of body cell mass [18]. A reduction in the amount of potassium in the total cell mass is likely to indicate a loss of protein [19]. The whole body counter method for calculating changes in body nitrogen depends on the assumption that nitrogen and potassium are lost in the same ratio as they exist in protoplasm [20]. The extent of loss of lean body mass observed with surgery appears to be related to severity of trauma [21]. In the present study the maximal decrease in TBK occurred 4 days after surgery in both groups. On the 7th day after operation the loss of cell mass remained significantly greater in the cold group than in the warmed group. This suggests that tissue breakdown began to be reversed more quickly in the warmed group.

It may be concluded from the present study that, when attempts are made to maintain patients normothermic during surgery, muscle tissue breakdown can be attenuated but not eliminated. The mechanism by which protein metabolism is affected has not yet been elucidated. Provision of thermoneutrality is known to decrease metabolic rate during the postoperative period [22]. In addition, it is not known how the rates of synthesis and breakdown of protein in muscle and other tissues are affected. Measurements of these processes should lead to a greater understanding of the physiopathology of nitrogen loss after injury and contribute to the development of more rational methods of modifying this loss in critically ill patients.

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Br. J. Anaesth. (1989), **63**, 283–286

PRESSOR AND CATECHOLAMINE RESPONSE TO NASAL INTUBATION OF THE TRACHEA

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It has been known since 1951 that intubation and laryngoscopy are associated with hypertension and tachycardia [1]. More recently , it has been demonstrated that an increase in plasma concentrations of adrenaline and noradrenaline occurs also in response to this stimulus [2, 3]. These changes may produce arrhythmias, myocardial ischaemia, cardiac failure and intracranial haemorrhage [4, 5]; thus most interest has centred on methods designed to attenuate these responses.

In a comparison of the stress response to laryngoscopy with and without intubation, Shribman and colleagues [6] found that laryngoscopy produced the major contribution to the stress response, and tracheal intubation *per se* contributed little additional effect. Althought this suggests that tracheal intubation without laryngoscopy may cause little sympathoadrenal stimulation, Smith [7] found that fibreoptic-assisted tracheal intubation produced greater cardiovascular stimulation than that following tracheal intubation using a laryngoscope.

Blind nasal intubation was reported by Prys-Roberts to produce no significant cardiovascular changes [4]. However, a subsequent study by Hartigan and colleagues [8] found that significant increases in arterial pressure occurred after nasal intubation without laryngoscopy.

In view of these conflicting findings, we have re-examined the cardiovascular responses to laryngoscopy and nasal intubation and compared the data with the changes associated with blind nasal intubation, in an attempt to assess the contribution produced by laryngoscopy *per se*. In addition, we have measured changes in plasma catecholamine concentrations as a further guide to changes in sympathoadrenal activity.

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SUMMARY

The catecholamine and cardiovascular responses to nasal intubation of the trachea with and without laryngoscopy have been compared in 23 patients allocated randomly to each treatment. Arterial pressure, heart rate and plasma concentrations of adrenaline and noradrenaline were measured before and after induction and at 1, 3 and 5 min after intubation of the trachea. There were significant increases in systolic and diastolic pressures after tracheal intubation in both groups. The values at 1 min after intubation were significantly higher in the group undergoing laryngoscopy and intubation compared with the group undergoing blind nasal intubation.

PATIENTS AND METHODS

We studied 28 adult patients (ASA I or II) presenting as in-patients for extraction of 3rd molar teeth under general anaesthesia. The study was approved by the local Ethics Committee, and informed consent was obtained from all patients.

Patients were premedicated with diazepam 10 mg orally, 1 h before operation. In the anaesthetic room, systemic arterial pressure and heart rate were measured using a COPAL semi-automated sphygmomanometer with printer (UA 251) with the cuff on the left arm. An 18-gauge cannula was placed in a vein in the right antecubital fossa to permit blood sampling for catecholamine assay. Ten millilitre of venous blood was withdrawn for baseline catecholamine assay before a 20-gauge cannula was inserted in the dorsum of the left hand for administration of drugs.

Anaesthesia was induced with thiopentone 3–4 mg kg^{-1} i.v., followed by suxamethonium 1.5 mg kg^{-1} i.v. to facilitate tracheal intubation. Anaesthesia was maintained with 67 % nitrous oxide and 1–1.5% enflurane in oxygen via a face mask attached to a Magill breathing system, with a fresh gas flow of 6 litre min^{-1} while the patients breathed spontaneously and 12 litre min^{-1} during artificial ventilation of the lungs. When the fasciculations caused by the suxamethonium had stopped, arterial pressure was measured, and a sample of blood taken for catecholamine assay.

The patients were allocated randomly to undergo tracheal intubation either by the "blind" nasal method, or by nasal intubation using a Macintosh laryngoscope and a Magill forceps when required. Blind nasal intubation was carried out in the following manner: a size 7.0 mm red rubber uncuffed nasotracheal tube, lubricated with K-Y jelly was introduced through the right nostril into the nasopharynx and then into the oropharynx. With the patient's neck well flexed, the head was extended on the neck and the nasotracheal tube advanced through the cords. This was achieved usually on the first two attempts. Correct placement was confirmed by observing symmetrical chest expansion, and by auscultation by a second experienced anaesthetist over both lung fields, and over the epigastrium. If any doubt existed regarding the location of the tube, a laryngoscope was used and the patient was excluded from the study.

Patients in the laryngoscopy group underwent tracheal intubation in a similar fashion, except that a laryngoscope was used in all, and Magill forceps when required. All tracheal intubations were carried out by the same anaesthestist (B.M.).

Manual ventilation of the lungs was continued until spontaneous ventilation had resumed, when the fresh gas flow was reduced to 6 litre min^{-1}. Capnography was used in the last two patients studied and this confirmed that the end-expired carbon dioxide was maintained at approximately 5–5.5% during the study period in these patients.

Venous samples were obtained, and arterial pressure and heart rate measured, at 1, 3 and 5 min after intubation. At the end of the study period, a throat pack was inserted and surgery proceeded after administration of an opioid i.v.

The 10-ml blood samples were collected into heparinized tubes, and centrifuged as soon as possible. The separated plasma was frozen at −70 °C until analysis for adrenaline and noradrenaline concentrations using a high pressure liquid chromatographic technique as described in previous studies from this department [3].

Data were analysed using analysis of variance followed by paired or unpaired Student's *t* test when appropriate; $P < 0.05$ was considered to be significant.

RESULTS

Twenty-eight patients were entered to the study, but one patient was withdrawn from the laryngoscopy group because of unexpected difficulties with intubation requiring bougies and repeated doses of neuromuscular blocker. Two patients in the blind nasal group were withdrawn during intubation because of difficulties requiring laryngoscopy and a further two patients in this group were withdrawn because of doubts regarding the location of the tube. Laryngoscopy was performed, and in one patient, the tube was resited in the trachea. All these patients were excluded from the study, and therefore data were analysed for a total of 23 patients, 12 in the blind nasal group, and 11 in the laryngoscopy group.

There were no significant differences between the two groups in age, weight and sex (table I).

At 1 min after intubation, the systolic pressure increased to values significantly greater in both groups ($P < 0.001$) than the pre-induction values. In the laryngoscopy group, this value was also significantly greater ($P < 0.01$) than the value after induction (table II). At 1 and 5 min after intubation, the systolic pressure in the laryngoscopy group was significantly greater ($P < 0.05$) than the blind nasal group (table II). Similarly, the diastolic pressure at 1 min after intubation

TABLE I. *Demographic data (Mean (SEM))*

	n	Age (yr)	Weight (kg)	Sex (M:F)
Blind nasal intubation	12	27.4 (1.4)	61.2 (2.8)	3:9
Laryngoscopy and nasotracheal intubation	11	26.0 (2.5)	64.1 (3.02)	3:8

TABLE II. *Cardiovascular variables and catecholamine concentrations (mean (SEM)). Significant differences:* *$P < 0.05$ *between groups;* ***$P < 0.001$ *compared with pre-induction values*

	Time after intubation (min)				
	Control	After intubation	1	3	5
Systolic AP (mm Hg)					
Blind	121.3	128.1	138.8***	120.0	107.5
	(4.8)	(5.0)	(4.9)	(4.3)	(3.8)
			*		*
Laryngoscopy	127.5	128.7	154.4***	131.8	122.3
	(3.9)	(4.7)	(4.5)	(4.6)	(5.1)
Diastolic AP (mm Hg)					
Blind	72.2	85.8	91.0***	79.3	69.6
	(2.4)	(2.4)	(3.2)	(2.9)	(2.6)
			*		
Laryngoscopy	77.3	91.4	103.1***	84.3	78.3
	(2.9)	(4.2)	(3.9)	(4.5)	(4.3)
Heart rate (beat min^{-1})					
Blind	79.8	112.3***	107.0	101.6	91.9
	(4.1)	(4.7)	(3.7)	(3.6)	(3.8)
Laryngoscopy	80.4	99.8***	101.8	103.3	100.7
	(5.6)	(6.1)	(5.7)	(3.6)	(3.6)
Adrenaline concn (pmol ml^{-1})					
Blind	0.82	0.96	1.27	0.78	0.78
	(0.14)	(0.17)	(0.31)	(0.14)	(0.78)
Laryngoscopy	0.94	1.07	1.30	1.24	1.08
	(0.2)	(0.16)	(0.28)	(0.26)	(0.23)
Noradrenaline concn (pmol ml^{-1})					
Blind	2.44	2.22	3.38	2.98	2.77
	(0.42)	(0.28)	(0.56)	(0.43)	(0.48)
Laryngoscopy	2.65	2.66	3.06	2.70	2.70
	(0.26)	(0.32)	(0.5)	(0.45)	(0.41)

increased to values significantly greater ($P < 0.001$) than pre-induction values. These were significantly greater ($P < 0.05$) in the laryngoscopy group compared with the blind nasal group (table II).

In both groups, heart rate increased significantly following induction ($P < 0.01$) and this difference persisted throughout the study period; at no time were there significant inter-group differences (table II).

Increases in plasma catecholamine concentrations were observed in both groups, but there were no significant changes within or between groups (table II).

DISCUSSION

Our results confirm the findings of the only previous study of this subject [8], notably that blind nasal intubation was associated with a significant increase in systolic and diastolic pressures. In addition, our data demonstrate that these changes in cardiovascular variables were significantly less than those produced when intubation was assisted by laryngoscopy. Increases in plasma catecholamine concentrations were seen also in both groups, although there were no significant differences between the two.

Shribman, Smith and Achola [6] investigated the sympathoadrenal responses to laryngoscopy alone and concluded that laryngoscopy contributed the major component to orotracheal intubation with laryngoscopy. Although our data do not suggest that laryngoscopy is the more potent stimulus, our study involved stimulation of the nose and nasopharynx by passage of a nasotracheal tube and, in addition, there were differences in patient selection and study design which make it difficult to compare directly the results of the present study with those of Shribman [6].

Several manoeuvres have been advocated to attenuate the pressor response to laryngoscopy and intubation [9]. It has been suggested that the pressor response to blind nasal intubation may be attenuated by the prior use of topical local anaesthesia to the airway [8]. This manoeuvre was not used in the present study, which was designed to investigate the unmodified responses to blind nasal intubation. However, previous studies of orotracheal intubation have suggested that application of local anaesthetic to the upper airway shortly before orotracheal intubation causes little attenuation of the pressor response [10, 11].

Avoidance of laryngoscopy by use of a fibreoptic laryngoscope has been advocated, but this was shown to be associated with a greater increase in arterial pressure than that observed with the use of a conventional laryngoscope [7].

Blind nasal intubation is another technique which avoids the use of a laryngoscope. However, the present study indicates that, although the accompanying pressor response is significantly less than that produced with concomitant laryngoscopy, manoeuvres designed to obviate laryngoscopy cannot prevent sympathoadrenal responses.

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LOCAL IRRITATION AFTER ADMINISTRATION OF DIAZEPAM IN A RECTAL SOLUTION

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SUMMARY

The extent of local irritation after rectal administration of diazepam in solution was studied in 24 adults (mean weight of 70 kg). The trial was randomized using a triple cross-over design. A burning sensation was reported in 60%, 12% and 0% of subjects up to 15 min after administration of diazepam 35 mg, diazepam 10 mg and placebo, respectively. Endoscopic assessment 24 h after medication showed mechanical irritation in three subjects and local irritation probably caused by diazepam, the vehicle, or both, in four. No correlation was found between subjective complaints and objective findings. Control endoscopy 7 days after medication revealed no pathology. It is suggested that a rectal solution of diazepam in doses up to 0.5 mg kg^{-1} is a safe form of medication in respect of irritation of the rectal mucosa.

The principal indications for rectal administration of diazepam are febrile convulsions in infants and children and for premedication in children. In the treatment of febrile convulsions in infants, anticonvulsant plasma concentrations were attained within 3–5 min of rectal administration of diazepam 0.7 mg kg^{-1} [1]. Sedation/relaxation has been achieved 4–6 min after the same dose given as premedication to 20 children [2]. Doses of diazepam 0.5–0.7 mg kg^{-1} given rectally have been advocated for adult patients undergoing outpatient oral surgery [3].

Local irritation following i.v. injection of diazepam has been described in several studies [4–7]. To our knowledge, local irritation after rectal administration of diazepam in solution has not been studied.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee and the Danish National Board of Health. Twenty-four healthy subjects (19 male) aged 21–30 yr (mean 25 yr) and of mean weight 70 kg (range 64–76 kg) gave informed consent for the study.

The trial was randomized using a triple cross-over design. The following medication was administered: diazepam 35 mg (Stesolid solution 10 ml in four rectal tubes—three tubes of 10 mg per 2.5 ml and one tube of 5 mg per 2.5 ml), diazepam 10 mg (Stesolid solution 2.5 ml in one rectal tube) and placebo (2.5 ml of Stesolid solution vehicle (propylene glycol–alcohol–water) in one rectal tube). Comparison of placebo with diazepam 10 mg was double-blind; when diazepam 35 mg was administered, only the investigator performing the endoscopic assessment of the rectum was blind to the treatment. The medications were administered at intervals of 35 days.

Subjects lay prone in a horizontal position before administration of the medication and for 15 min after the administration, after which they lay supine. While holding the rectal tube vertically, the investigator introduced the entire length of the nozzle (5 cm) into the rectum, and the contents of the tube were squeezed out. The tube was firmly compressed while the nozzle was withdrawn.

Twenty-four hours after medication, all subjects were assessed endoscopically by the same investigator. No control endoscopy was performed before the study. At the time of endoscopy

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the subjects were asked if they had experienced any local irritation during administration of medication or afterwards.

RESULTS

The mean doses of diazepam received were 0.14 mg kg^{-1} (after diazepam 10 mg) and 0.5 mg kg^{-1} (after diazepam 35 mg).

Endoscopic assessment

In 19 subjects, endoscopy revealed normal rectal mucosa. Seven findings in the remaining five subjects were regarded as pathological. One subject exhibited abnormalities after all three medications. Bruising or redness was taken to be caused by mechanical manipulation, and petechiae were taken to be drug-induced (table I).

Volunteer No. 7. A reddish area of approximately 0.5 cm × 0.5 cm was found in the anterior part of the rectum, 5 cm from the anus, after the administration of diazepam 35 mg. The investigator concluded that the cause was mechanical manipulation of the rectal introducer.

TABLE I. *Numbers of subjects with endoscopic or subjective complaints after rectal administration of diazepam or placebo. M = Local irritation from mechanical manipulation; D = Local irritation from drug or vehicle; A = Burning sensation in the rectum up to 15 min after administration; B = Stinging sensation in the rectum up to 15 min after administration*

Subject	Diazepam 35 mg	Diazepam 10 mg	Placebo
1	A	—	—
2	—	—	—
3	B	—	—
4	A	A	—
5	A	—	—
6	—	—	—
7	M,A	—	—
8	A	—	—
9	A	A	—
10	—	—	—
11	A,B	A	—
12	—	—	—
13	M,B	D	D
14	—	—	—
15	B	—	—
16	B	M	—
17	D,A	—	—
18	—	—	—
19	A,B	—	—
20	—	—	—
21	—	—	—
22	—	—	—
23	D,A	—	—
24	A	—	—

Volunteer No. 13. Bruising, 0.5 cm × 2 cm, appeared in the anterior part of the rectum, 6 cm from the anus, after administration of diazepam 35 mg. Petechiae were found in the anterior part of the rectum, 5–6 cm from the anus, after administration of diazepam 10 mg. The same clinical picture was found (petechiae 5–8 cm from the anus in the anterior part of the rectum) after administration of placebo. A control endoscopy 7 days after administration of diazepam 10 mg showed no abnormalities. The investigator concluded that the bruising found after the administration of diazepam 35 mg was caused by mechanical manipulation. The petechiae occurring after administration of diazepam 10 mg and placebo were probably the result of local irritation from the drug or vehicle.

Volunteer No. 16. Bruising 0.5 cm × 0.5 cm was found in the posterior part of the rectum, 5 cm from the anus, after administration of diazepam 10 mg. The investigator concluded that the cause was mechanical manipulation.

Volunteer No. 17. Petechiae were found in the anterior and posterior part of the rectum, 5–10 cm from the anus, after administration of diazepam 35 mg. A control endoscopy 7 days later revealed no abnormality. This was thought to be the result of local irritation caused by the drug.

Volunteer No. 23. One of the investigators noted perianal irritation of the skin *before* the medication with diazepam 35 mg. At the endoscopic assessment a slight irritation was found throughout the rectal mucosa. Control endoscopy 7 days later showed no abnormality. The blinded investigator performing the endoscopies was unable to conclude if the drug was the cause.

Subjective complaints

Two subjective complaints were stated after questioning: a burning sensation in the rectum immediately after administration (this did not last for more than 15 min); a stinging sensation of the rectum immediately after administration (this did not last for more than 15 min).

No other complaints were recorded in the 24 h between medication and endoscopic assessment.

Of the 24 subjects, 15 complained of burning or stinging sensations, or both, after administration of diazepam 35 mg (10 ml), whereas only three complained of the same after administration of diazepam 10 mg (2.5 ml) (table I). The frequency of local irritation was significantly higher (McNemar's test, $P \leqslant 0.0005$) in the 35-mg group than in the 10-mg group.

DISCUSSION

A study in which the *vehicle* (propylene glycol–alcohol–water) in the Stesolid rectal solution was given to 10 volunteers suggested that irritation was more pronounced when the volume of the vehicle was increased from 2.5 ml to 10 ml [8].

In 60% of our subjects 10 ml of diazepam (35 mg) caused burning or stinging sensations, or both, in the rectum up to 15 min after administration. In contrast, 12% complained of a burning sensation after administration of 2.5 ml of diazepam (10 mg) and none after administration of placebo vehicle 2.5 ml.

The frequency of subjective complaints must be viewed as a result of direct questioning. Administration of diazepam 35 mg necessitates four rectal tubes, whereas only one was needed in the other phases of the study. Thus bias may also play a role, as the subjects knew they were receiving a large dose of diazepam.

Endoscopic assessment of the rectal mucosa after 24 h showed that, of 144 administrations, mechanical irritation occurred with three. In two of the volunteers, this was found after four administrations in the same session, and in the third, after a single administration. It may be concluded, therefore, that slight mechanical irritation of the rectal mucosa may be expected in 2% (three of 144) of adults when drugs are administered by means of a rectal tube.

Four subjects had reversible local irritation of the rectal mucosa, which was caused probably by diazepam, the vehicle, or both: two after administration of diazepam 35 mg (10 ml), one after administration of diazepam 10 mg (2.5 ml), and one subject after administration of placebo (2.5 ml).

It is not clear if the local irritation was caused by the vehicle alone or the combination of vehicle and diazepam. No correlation was found between subjective complaints and pathological findings at endoscopic assessment. We conclude that a rectal solution of diazepam in doses up to 0.5 mg kg^{-1} in adults is a safe form of medication in respect of rectal irritation, and that burning or stinging sensations lasting up to 15 min after medication may be expected.

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Br. J. Anaesth. (1989), **63**, 290–295

EFFECTS OF NITROUS OXIDE AND VOLATILE ANAESTHETICS ON CEREBRAL BLOOD FLOW

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SUMMARY

Nitrous oxide and halogenated anaesthetic agents are often administered concurrently during neuroanaesthesia. To assess the interactive effects of these agents on cerebral blood flow (CBF), we have measured CBF by ^{14}C-iodoantipyrine autoradiography, in normocapnic rats receiving either 0.5 or 1.0 MAC of volatile agent alone (halothane or isoflurane) or 0.5 MAC of volatile agent + 0.5 MAC nitrous oxide. CBF (global and regional) was significantly greater at 1.0 MAC compared with 0.5 MAC, regardless of how 1.0 MAC was achieved (agent alone or agent + nitrous oxide) ($P < 0.05$). The addition of 0.5 MAC nitrous oxide to 0.5 MAC halothane resulted in flows similar to those produced by 1.0 MAC halothane alone. In contrast, the addition of nitrous oxide to 0.5 MAC isoflurane resulted in flow values significantly greater than those measured during 1.0 MAC isoflurane alone. We conclude that the use of nitrous oxide, as opposed to an increased dose of volatile agent, has no advantage in respect of minimizing anaesthetic-induced increases in cerebral blood flow.

Nitrous oxide is a common component of neurosurgical anaesthesia, partly because it facilitates rapid emergence from anaesthesia [1] and partly because nitrous oxide is often thought to have modest effects on the brain [2, 3]. Volatile anaesthetics are known to increase cerebral blood flow (CBF) and, potentially, intracranial pressure (ICP) [4–6] and, to minimize this risk, many clinicians use a combination of nitrous oxide and volatile agent, thereby reducing the required concentration of the volatile drug. However, some studies have shown that the effects of nitrous oxide on CBF are substantial [7–14] and that it may also have important effects on ICP [15, 16].

We have compared the relative effects on CBF of increasing the concentration of volatile agent from 0.5 to 1.0 MAC with an equivalent anaesthetic dose (0.5 MAC) of nitrous oxide, utilizing autoradiographic methods in the rat.

MATERIALS AND METHODS

This study was approved by our institutional Animal Care and Use Committee. Fifty-two male Sprague–Dawley rats weighing between 310 and 390 g were anaesthetized with either 1.5% halothane or 2.0% isoflurane allocated randomly and 33% oxygen in nitrogen. Tracheotomy was performed and the lungs ventilated mechanically with a tidal volume of 2.5 ml at a rate of 60 b.p.m. Catheters were inserted into a femoral artery and vein via surgical incisions under local anaesthesia with 2.0% lignocaine. The arterial catheter was connected to a transducer for continuous measurement of arterial pressure and the venous catheter was used for administration of drugs and fluids. Heparin 200 iu and tubocurarine 2 mg were administered i.v. to each rat. A surgical preparation interval of 35 min (measured from the start of induction) was allowed.

Following surgical preparation, rats were allocated to one of six groups: two to receive 0.5 and four to receive 1.0 MAC anaesthesia. For the 0.5 MAC groups, halothane or isoflurane concentrations (delivered) were reduced to 0.55% and 0.70%, respectively. In two of the 1.0 MAC groups, rats received 1.10% halothane or 1.40% isoflurane and 70% nitrogen in oxygen, and in the remaining two 1.0 MAC groups they received the 0.5 MAC equivalent of either volatile agent

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Accepted for Publication: March 18, 1989.
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+70% nitrous oxide in oxygen. In all cases, the volatile agent administered remained the same as that used for surgical preparation. MAC values in the Sprague–Dawley rat for halothane and isoflurane were taken from White, Johnston and Eger [17] and for nitrous oxide (140%) from Difazio and colleagues [18]. After the anaesthetic regimens had been established, animals remained anaesthetized at steady-state delivered concentrations for an additional 55 min. Anaesthetic concentrations were monitored by a Puritan Bennett Model 222 anaesthetic agent monitor (Wilmington, Mass.) sampling gas from the expiratory limb of the anaesthetic system. Previous work in our laboratory has indicated that this technique reflects end-tidal concentrations with an accuracy of approximately 97% after 55 min of exposure to 1.0 MAC delivered volatile agent [19].

During this equilibrium period, the ventilator was adjusted to maintain normoxia (Pa_{O_2} = 14.6–18.6 kPa) and normocapnia (Pa_{CO_2} = 5.1–5.6 kPa). Arterial blood was analysed at 15-min intervals with an automated blood-gas analyser (Radiometer ABL-2, Copenhagen, Denmark). Body temperature was monitored via a rectal probe and maintained within the range 36.5–37.5 °C by surface heating or cooling. Mean arterial pressure (MAP) was monitored continuously and maintained within the range 90–100 mm Hg by infusion of donor whole rat blood as required.

CBF determination

Following the 55 min exposure to respective anaesthetic agent regimens, animals were given 1 ml of donor blood to compensate for subsequent blood loss during arterial sampling. Final MAP and arterial blood-gas values were recorded, and ^{14}C-labelled iodoantipyrine (^{14}C-IAP, specific activity 60 mCi $mmol^{-1}$, New England Nuclear, Boston, Mass.) 75 μCi kg^{-1} was infused i.v. at a constant rate over 45 s via an infusion pump. During this time, 10 discontinuous 20-μl arterial blood samples were collected for later determination of arterial isotope activity. Immediately upon completion of isotope infusion, animals were decapitated, the brains removed rapidly, and frozen in 2-methyl butane (−40 °C). If brain removal required more than 2 min, the brain was discarded. Timed arterial blood samples were placed separately on chromatography paper, dried for 24 h, and eluted for an additional 24 h in a mixture of water 1 ml and liquid scintillation mixture 9 ml (Beckman, Fullerton, CA.). Radioactivity was determined by liquid scintillation counting using an external quench correction.

Autoradiography and image analysis

Frozen brains were cut in 20-μm thick serial coronal sections with a cryostat at −20 °C. Quadruplicate sections taken at 240-μm intervals were mounted on glass slides, dried for 5 min on a 50 °C hot plate, and exposed to Kodak SB-5 autoradiographic film for seven days in an x-ray cassette with seven ^{14}C-methylmethacrylate standards (Amersham, Arlington Hts, Ill). Images of eight brain sections were chosen from each animal for further analysis based upon standardized anatomical landmarks over the rostral–caudal axis [19]. These autoradiographic images were converted to digitized optical density images on a scanning microdensitometer system (Eikonix-Kodak, Bedford, Mass.) with a camera aperture of 100 μm and a fixed focal length. Optical densities from autoradiographic images, standard radioactivity values in tissue equivalents and timed arterial blood radioactivity values were entered on a computer system. For optical density recalculation from image grey levels to CBF values, we utilized the equations developed by Reivich and colleagues [20] and modified by Sakurada and co-workers [21]; mathematical operations were performed using the National Institutes of Health cerebral blood flow program (C. Patlak, Bethesda, Maryland).

Data analysis

Individual digitized CBF images were pseudocolour enhanced and displayed on a cathode ray screen. By an operator-controlled cursor, regions of interest were outlined and mean CBF was determined within each region, together with the area of that region in pixel units. Three primary regions of interest were hemisphere, neocortex, and subcortex. Subcortex was defined as the total hemispheric area minus the area of the cortical mantle. Olfactory and entorhinal cortices are limbic structures and were included in subcortex [22]. Ventricular spaces were subtracted before performance of CBF calculations.

For each section level within each animal, area-weighted hemispheric, neocortical and subcortical blood flow values were determined. These values were averaged over all eight sections evaluated, yielding mean values for each region of interest

TABLE I. *Physiological values (mean (SD)) measured immediately before the determination of CBF as a function of anaesthetic regimen. No significant differences were observed between groups*

	n	Total MAC	Pa_{CO_2} (kPa)	Pa_{O_2} (kPa)	Arterial ph	MAP (mm Hg)	Temp. (°C)
Group A							
0.5 MAC halothane	8	0.5	5.2 (0.2)	16.4 (2.5)	7.38 (0.03)	97 (5)	36.9 (0.18)
Group B							
0.5 MAC isoflurane	7	0.5	5.3 (0.3)	15.7 (2.3)	7.38 (0.04)	97 (4)	37.0 (0.16)
Group C							
1.0 MAC halothane	8	1.0	5.3 (0.3)	17.8 (4.3)	7.38 (0.04)	95 (4)	36.9 (0.15)
Group D							
1.0 MAC isoflurane	7	1.0	5.2 (0.2)	14.6 (2.8)	7.37 (0.04)	96 (4)	37.0 (0.17)
Group E							
0.5 MAC hal. + N_2O	8	1.0	5.2 (0.3)	16.1 (2.9)	7.38 (0.03)	94 (5)	36.9 (0.15)
Group F							
0.5 MAC iso. + N_2O	8	1.0	5.3 (0.2)	17.0 (3.3)	7.38 (0.04)	94 (4)	37.0 (0.17)

(hemisphere, neocortex and subcortex). Mean CBF values for each region of interest were compared between the six anaesthetic groups by one-way analysis of variance. Specific intergroup differences were identified using a Newman–Keuls test for multiple comparisons where indicated by a significant *F* ratio.

Physiological values were compared between anaesthetic groups by one-way analysis of variance. One animal from the 1 MAC isoflurane group was excluded from analysis because of Pa_{CO_2} values deviating by more than two standard deviations from the group mean. One animal from the 0.5 MAC isoflurane group was excluded because of a brain removal time exceeding 2 min. Values throughout are given as mean (SD) with significance assumed when $P < 0.05$.

RESULTS

No significant differences were noted between anaesthetic groups with respect to baseline Pa_{O_2}, Pa_{CO_2}, MAP or body temperature values (table I).

Hemispheric blood flow (area-weighted mean value of eight rostral–caudal coronal sections) was similar for halothane and isoflurane at both 0.5 and 1.0 MAC concentrations (table II; fig. 1). For each agent, a significantly greater flow value was observed at 1.0 MAC compared with 0.5 MAC ($P < 0.05$). The addition of 70% nitrous oxide (0.5 MAC) to 0.5 MAC isoflurane resulted in hemispheric flow values greater than those observed at either 0.5 or 1.0 MAC isoflurane alone ($P < 0.01$).

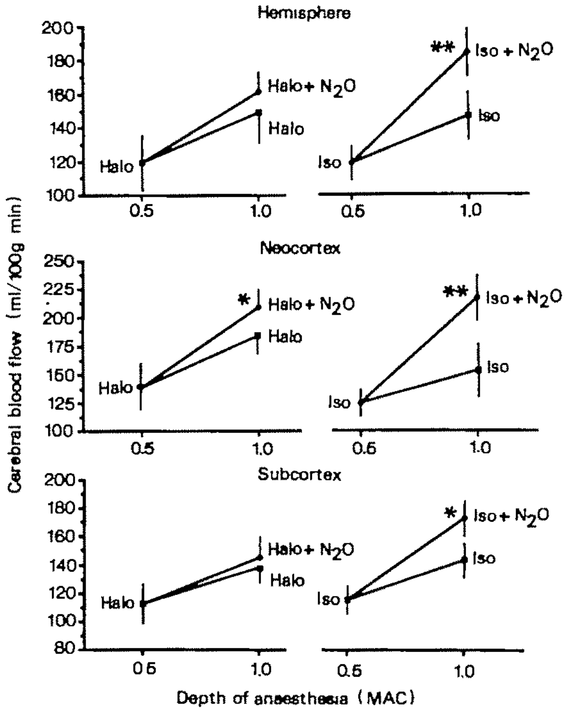

FIG. 1. Cerebral blood flow (mean, SD) in respective regions as a function of depth of anaesthesia for the respective anaesthetic regimens. Mean hemispheric "global" blood flow taken as the area-weighted average from eight coronal sections over the rostral-caudal axis. $*P < 0.05$; $**P < 0.01$, comparing blood flow during exposure to volatile agent at 1 MAC with volatile agent at 0.5 MAC + 70% nitrous oxide. In all cases, the addition of 70% nitrous oxide to 0.5 MAC volatile agent increased blood flow ($P < 0.01$). In the neocortex only, flow was greater with halothane alone than with isoflurane alone at both 0.5 and 1.0 MAC.

TABLE II. *Mean (SD) blood flow values (ml/100 g min) in hemispheric, neocortical and subcortical regions for each anaesthetic group, presented as values averaged over eight area-weighted coronal sections. For statistical purposes, the anaesthetic groups are labelled A–F. In the body of the table, A–F indicate that the value shown differs significantly* ($P < 0.05$) *from the value obtained within the same region in the groups indicated*

	n	Total MAC	Hemispheric		Neocortical		Subcortical	
Group A 0.5 MAC halothane	8	0.5	120 (16)	(C, D, E, F)	139 (10)	(B, C, E, F)	113 (14)	(C, D, E, F)
Group B 0.5 MAC isoflurane	7	0.5	119 (10)	(C, D, E, F)	125 (11)	(A, C, D, E, F)	116 (10)	(C, D, E, F)
Group C 1.0 MAC halothane	8	1.0	150 (16)	(A, B, F)	185 (16)	(A, B, D, E)	139 (17)	(A, B, F)
Group D 1.0 MAC isoflurane	7	1.0	147 (12)	(A, B, F)	153 (19)	(B, C, E, F)	144 (12)	(A, B, F)
Group E 0.5 MAC hal. + N_2O	8	1.0	162 (12)	(A, B, F)	210 (15)	(A, B, C, D)	146 (12)	(A, B, F)
Group F 0.5 MAC iso. + N_2O	8	1.0	185 (14)	(A, B, C, D, E)	214 (22)	(A, B, C, D)	174 (12)	(A, B, C, D, E)

The combination of isoflurane + nitrous oxide also yielded hemispheric flow values greater than any of the groups receiving halothane or halothane plus nitrous oxide ($P < 0.05$). In contrast, while the combination of 70% nitrous oxide and 0.5 MAC halothane resulted in hemispheric flow values greater than those observed at 0.5 MAC halothane alone, the flow values observed in this group were not different from those receiving 1 MAC halothane alone.

In the neocortex, a different pattern emerged. At 0.5 MAC, cortical blood flow was greater in rats receiving halothane compared with those given isoflurane ($P < 0.01$). The distinction between the cortical CBF effects of these two agents was preserved at 1.0 MAC. For both agents, neocortical flow was increased when the anaesthetic concentration was increased from 0.5 to 1.0 MAC ($P < 0.05$). When nitrous oxide was added to 0.5 MAC of either volatile agent, cortical flow was significantly greater than values observed at 0.5 or 1.0 MAC for each agent alone (table II).

In the subcortex, the pattern matched more closely that observed in the hemisphere as a whole. Flow values at 0.5 and 1.0 MAC were similar between volatile anaesthetic agents at each depth of anaesthesia. The addition of nitrous oxide again significantly increased flow relative to 0.5 MAC values for each volatile agent, but only in the case of isoflurane did the additive effect of nitrous oxide + 0.5 MAC isoflurane cause flow to be greater than 1 MAC volatile anaesthetic alone.

DISCUSSION

The purpose of this investigation was to determine the relative magnitude of CBF response when an increase in depth of anaesthesia was achieved with either volatile anaesthetic alone or by the addition of an equivalent anaesthetic dose of nitrous oxide. Our results indicate that, for both regional and global CBF, there was an increase following the addition of nitrous oxide which was as great as that which occurred if a similar anaesthetic depth had been achieved with volatile agent alone. In most instances, the addition of 70% nitrous oxide resulted in greater CBF than did the addition of 0.5 MAC volatile agent. This was particularly true for isoflurane.

Several other studies have investigated the interactive effects of nitrous oxide and volatile anaesthetics on cerebral blood flow. Using the radioactive microsphere technique in swine, Manohar and Parks [9, 10] observed that the addition of 0.5 MAC nitrous oxide to 0.5 MAC halothane or isoflurane resulted in a greater blood flow than did a 1 MAC dose of either agent alone. The interpretation of these results was difficult, however, because of marked variations in mean arterial pressure (MAP) occurring between anaesthetic groups: MAP was significantly greater in those animals receiving nitrous oxide. Although cerebral autoregulation would be expected to be largely intact, and correcting for this discrepancy at 1.0 MAC anaesthesia [23], this has not been evaluated either in swine or under the combined influence of nitrous oxide and volatile agent. Thus in the present study, we have kept MAP constant in all groups and we observed that the CBF effects of nitrous oxide were as great as those associated with a similar dose of halothane or isoflurane. Our data are therefore consistent with the conclusions of Manohar and Parks [9, 10] that the combination of nitrous oxide with volatile agents caused a substantial increase in CBF. However, while Manohar and Parks found that the nitrous oxide effect was more pronounced in the presence of halothane than isoflurane, the converse was observed in our study. This may be a reflection of species differences or variations in methodology.

Drummond, Scheller and Todd [12] have also investigated the CBF effect of nitrous oxide during background anaesthesia with halothane or isoflurane in the rabbit. As was observed by Manohar and Parks [6, 7], the addition of nitrous oxide to 0.5 or 1.0 MAC of either agent resulted in increased CBF. Although Drummond and colleagues maintained constant MAP by i.v. infusion of angiotensin II, they used a hydrogen clearance technique for measurement of cortical CBF. This technique measures flow in a tissue volume of approximately 1 mm in diameter about the implanted platinum electrode [24], and it has been shown that conclusions drawn on anaesthetic effects on cerebral blood flow are dependent upon where CBF is measured in the brain. For example, while 1 MAC halothane and 1 MAC isoflurane have nearly identical effects on global CBF, halothane causes a greater increase in cortical CBF than isoflurane [19]. It is possible, therefore, that the findings of Drummond and colleagues may only apply to the cortex and not to the brain as a whole. However, our data failed to confirm this hypothesis. On both a global level (area-weighted mean of eight hemispheric values taken over the rostral–caudal extent of the brain) and a regional basis (cortex and subcortex), an increase in CBF was observed with the addition of nitrous oxide at least as great as that caused by doubling the volatile anaesthetic concentration.

Does this study have any clinical relevance for the patient with intracranial hypertension? It is well known that nitrous oxide has been used for a very large number of craniotomies with no apparent evidence of worsened neurological outcome, except in the notable case of pre-existing pneumocephalus. However, we know that administration of nitrous oxide (particularly in combination with volatile agents) may cause increases in CBF and intracranial pressure which may or may not be responsive to hyperventilation [13, 25]. This suggests that it may be reasonable, at present, to continue to use nitrous oxide during craniotomy, but clinical studies and our data suggest that, in some patients, it may be more appropriate to discontinue nitrous oxide before the use of volatile agent. In addition, its use may not be beneficial when operative conditions arise such as uncontrollable brain bulk.

The mechanism whereby nitrous oxide increases CBF may be direct vasodilatation, but other data suggest a more complex phenomenon. Nitrous oxide alone has little or no effect on either CBF or the cerebral metabolic rate for glucose utilization in the rat [3, 26] and it is unclear why its effects on CBF are so pronounced in the same species in the presence of a halogenated anaesthetic agent. We do know that effects of volatile anaesthetics on CBF are to a large extent mediated by their respective effects on cerebral metabolism [27]. We may postulate that, if this relationship (coupling of flow and metabolism) is perturbed by nitrous oxide, the resultant CBF might be increased. This would be consistent with our observation that the addition of nitrous oxide to 0.5 MAC isoflurane—a greater cerebral metabolic depressant than halothane—had more profound effects on CBF than the combination of nitrous oxide with halothane. This hypothesis remains untested, but warrants investigation.

ACKNOWLEDGEMENTS

Dr Warner is a Parker B. Francis Investigator in Anesthesiology. This study was supported in part by U.S.P.H.S. Grants R29 GM39771 awarded to Dr Warner and R01 NS24517 to Dr Todd.

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ENFLURANE-INDUCED BURST DISCHARGE OF HIPPOCAMPAL CA1 NEURONES IS BLOCKED BY THE NMDA RECEPTOR ANTAGONIST APV

M. B. MACIVER AND J. J. KENDIG

SUMMARY

The basis for the hyperexcitability and seizure activity associated with enflurane anaesthesia was investigated using extracellular and intracellular recording in rat hippocampal brain slices. Enflurane produced seizure-like burst discharges in CA1 pyramidal neurones, accompanied by depressed field potential amplitudes and a reduced threshold for synaptically evoked population spikes. However, threshold for action potentials evoked by intracellular current injection did not change, nor did action potential amplitude, duration or spike frequency accommodation in single neurones. Enflurane 2.0 vol% hyperpolarized CA1 neurones (3.1 (SD 1.3)mV), decreased membrane conductance (12 (6)% below control), and depressed EPSP amplitudes (34% of control) ($P < 0.01$). Enflurane appeared to enhance both intrinsic and synaptically mediated inhibitory potentials. The N-methyl-D-aspartate (NMDA) receptor antagonist amino-phosphonovalerate (APV) 5–20 μmol litre^{-1} completely blocked seizure-like burst discharge of CA1 neurones in the presence of enflurane, and the enflurane-induced reduction of population spike threshold; it did not alter anaesthetic depression of EPSP amplitude. Thus enflurane-induced burst discharge of CA1 neurones appeared to involve an enhancement of excitatory synaptic transmission rather than depression of intrinsic or synaptic inhibition.

The inhalation anaesthetic enflurane produces seizure-like burst discharge activity in the cortical EEG during anaesthesia [1, 2]. Enflurane-induced seizure activity has been associated with both excitation and depression of the CNS [3]. Concentration-dependent biphasic actions have been described *in vivo* [4] and on synaptic responses recorded from neurones in the *in vitro* hippocampal brain slice preparation [5]. Enflurane-induced seizure-like burst discharge of hippocampal CA1 pyramidal neurones is preserved also in the slice preparation [6]. Thus it should be possible to gain a more detailed understanding of the CNS excitatory/depressant actions which accompany enflurane-induced seizure activity by examining the actions of enflurane on individual CA1 pyramidal neurones *in vitro*.

The hippocampal brain slice preparation is a useful preparation for investigation of convulsant actions and epileptogenic mechanisms [7–9]. Three distinct classes of convulsants have been distinguished, according to different mechanisms of action (fig. 1). The first class of agents includes "traditional" convulsants such as penicillin, bicuculline and picrotoxin which act, at least in part, to depress GABA-gated chloride currents in pyramidal neurones [10]. Convulsants in the second class increase neuronal excitability by depressing intrinsic potassium currents which normally regulate (inhibit) action potential discharge activity. This group includes the convulsants 4-aminopyridine, apamin and tetraethylammonium [11, 12]. A third class of convulsant agents has been shown to increase synaptically evoked calcium currents mediated by excitatory amino acid receptors [13–15]. This class includes kainic acid, folates and N-methyl-D-aspartate (NMDA) (a synthetic glutamate analogue). Seizure discharge induced by these agents can be blocked by the NMDA receptor antagonist amino-phosphonovalerate (APV) [14–16].

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We investigated actions of enflurane at these three possible convulsant sites using extracellular and intracellular electrophysiological recordings from neurones in the CA1 region of rat hippocampal slices.

MATERIALS AND METHODS

Preparation

Experiments were conducted on 38 hippocampal slices from male Sprague–Dawley rats (150–250 g). Fourteen slices were used for enflurane experiments and six were used for each of four other anaesthetics (isoflurane, halothane, methoxyflurane and pentobarbitone). Each slice was exposed to only one or two concentrations of a single anaesthetic. Rats were anaesthetized with diethyl ether, the heart stopped by a blow to the back of the thorax, and the brain removed rapidly and placed in pre-cooled (10 °C) artificial cerebrospinal fluid (aCSF). Following dissection of the dentate–hippocampal formation, transverse slices of hippocampus were cut using a McIlwain tissue chopper (400 µm, Mickel Lab. Eng. Co., U.K.). Slices were maintained on a nylon mesh screen at the gas–liquid interface in a chamber based on the design of Richards and Tegg [17]. Oxygenated (95 % oxygen–5 % carbon dioxide) and prewarmed aCSF was perfused continuously through the chamber at a rate of 0.25–0.5 ml min^{-1}, to achieve a temperature of 35 °C surrounding the slices. The aCSF had the following composition (mmol litre^{-1}): NaCl 134; KCl 4.5; $CaCl_2$ 1.6; KH_2PO_4 1.25; $MgSO_4$ 2; $NaHCO_3$ 16; dextrose 10. This solution was modified from that of Richards, Russell and Smaje [18] by adjusting calcium and potassium concentrations to correspond to values measured *in vivo* [19]. Following oxygenation and prewarming, the aCSF solution had a pH of 7.2–7.4.

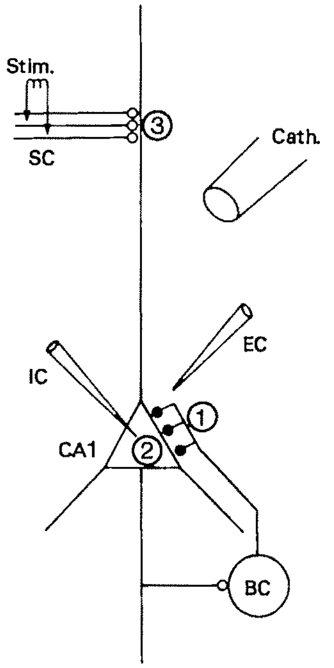

FIG. 1. Schematic diagram showing three potential sites of convulsant action. 1 = Depression of a basket cell (BC) to CA1 GABA-mediated inhibitory synapse; 2 = depression of intrinsic CA1 neurone inhibitory K^{+} currents; 3 = enhancement of a glutamate-mediated excitatory synapse. Placement of stimulating (Stim.) and recording electrodes (IC = intracellular; EC = extracellular) for measuring synaptically evoked responses from Schaffer collateral (SC) input fibres to CA1 pyramidal neurones is shown. Concentrations of enflurane in the gas phase were monitored continuously by a sampling catheter (Cath.) placed within 1 mm of the impaled neurone.

Electrophysiology

The arrangement of stimulating and recording electrodes is shown diagrammatically in figure 1. A bipolar tungsten stimulating microelectrode was placed on Schaffer-collateral fibres to activate electrically the excitatory synaptic inputs to CA1 pyramidal neurones. Extracellular field potentials were recorded via glass fibre-fill recording electrodes (filled with aCSF, resistance 0.5–5.0 MΩ) placed at the border between stratum pyramidale and stratum oriens to measure synaptically evoked field potentials at the cell soma level. Recorded signals were amplified (× 1000), filtered (1 Hz to 10 kHz, bandpass), and stored digitally for later analysis. Records shown are averages of 10 individual field potentials recorded at a stimulus frequency of 0.08 Hz. Population EPSP amplitude was measured as the peak positivity and population spike (PS) amplitude was measured from threshold to peak negativity. Criteria for accepting a slice included stable population spikes of at least 4 mV amplitude evoked by stimuli of low intensity (< 10 V).

For intracellular recording, glass fibre-fill recording electrodes (1.0 mm o.d., thin wall, Sutter Instruments, U.S.A.) were pulled on a P-80/PC Flaming Brown micropipette puller. Electrodes were filled with potassium acetate 4 mol litre^{-1} and bevelled to produce tip resistances of 80–140 MΩ. A modified Getting microelectrode bridge amplifier (Model 5A) was used to inject current and measure potential changes across CA1 neurone somatic membrane. Recorded signals were amplified (× 100) and stored digitally for later analysis. Membrane conductance was measured by injecting hyperpolarizing current pulses through the intracellular recording electrodes. Resting membrane potential was monitored continuously, recorded on a chart recorder, and absolute values determined by withdrawing the electrode from impaled neurones following each experiment. Criteria for accepting the results from a cell include a stable resting potential of at least −60 mV. Ten cells were examined; mean control resting potential was −67.5 (SD 2.7) mV.

Administration and analysis of enflurane

Enflurane was applied as a vapour via the prewarmed and humidified oxygen–carbon dioxide gas stream above the slices, using a calibrated commercial vaporizer (Foregger, mod. DRV3). Vapour concentrations were applied for up to 30 min to ensure that equilibrium was achieved. Steady-state effects on PS amplitudes were observed consistently after 20 min for all concentrations studied. Particular care was taken to examine concentration ranges which are relevant to anaesthesia (enflurane MAC = 1.8–2.0 vol %, in rats) [20]. The other volatile anaesthetics were applied in similar fashion; pentobarbitone was delivered by dissolving it in the perfusate to the required concentration (100 μmol litre^{-1}).

Accurate measurements of volatile anaesthetic concentrations in the vapour phase were obtained using an infra-red absorption monitor (Puritan-Bennett Co., Mod. AAM222). Sample gas was drawn continuously from the tissue chamber at a site < 1.0 mm above the tips of the stimulating electrode in the brain slice. Chamber concentrations reached equilibrium within 5 min of adding the anaesthetic to the gas stream. An approximation of the corresponding aCSF concentrations of enflurane (in mmol litre^{-1}) can be obtained from MacIver and Roth [5], together with complete concentration–response curves. Enflurane and isoflurane were obtained from Anaquest Inc., methoxyflurane from Abbott Laboratories, halothane from Ayerst Laboratories Inc., and pentobarbitone was obtained from BDH Chemicals. APV (a racemic mixture of the D and L isomers) was obtained from Sigma Chemical Co. All chemicals used in the aCSF were reagent grade or better and were obtained from J. T. Baker Chemical Co.; water for solutions was HPLC and spectrophotometry grade from EM Science Inc.

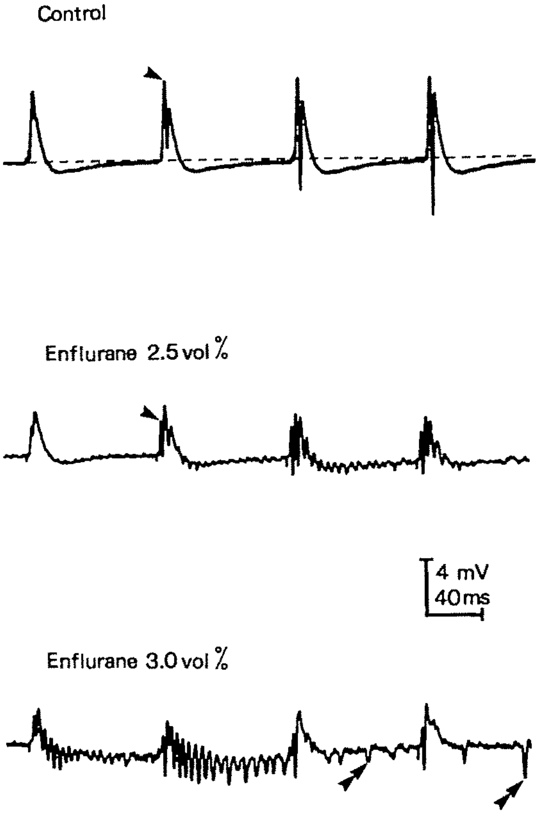

FIG. 2. Field potential records showing potentiation of population spikes at 8 Hz stimulus frequency. Enflurane reduced the amplitude of synaptically evoked field potentials but appeared to increase CA1 neurone excitability, as indicated by a reduction in population spike threshold (arrow) and multiple burst discharges produced in the presence of the anaesthetic. Seizure-like burst discharge of population spikes was more pronounced at higher concentrations (e.g. 3.0 vol %) and was accompanied by spontaneous field discharges (double arrow). Population spike potentiation was not altered by enflurane.

RESULTS

Burst firing

The field potential records in figure 2 illustrate enflurane-induced burst discharge of CA1 neurones. In control conditions without enflurane, low-intensity stimulation (6 V, 50 μs) of Schaffer collateral inputs resulted in minimal (threshold) discharge of CA1 neurones, as evident by a barely detectable population spike in the first response to a train of four identical stimuli at

8 Hz. Population spikes increased in amplitude in response to each successive stimulus in the train (potentiation), achieving near maximal (> 95%) amplitude following the fourth stimulus. The apparent threshold for population spike discharge (voltage of the inflection on the population EPSP) increased during the stimulus train, as did the negative potential following each response. Enflurane produced two different concentration-dependent effects on the population spike. Low concentrations of 0.5–1 MAC (approximately 2.0 vol% in rat) depressed population spike amplitudes, while higher concentrations resulted in multiple population spike (burst) discharges (fig. 2). The burst discharge activity was associated with a reduction in population spike threshold (arrow in figure 2) and amplitude. In the presence of high concentrations of enflurane (3.0 vol%), population spike discharges could follow synaptically evoked responses by long latencies (100–500 ms; double arrows in figure 2).

Since enflurane is the only clinically used inhalation agent which produces seizure-like burst activity in the cortical EEG during anaesthesia, it was of interest to compare actions of some other anaesthetics with respect to their ability to induce burst discharge of CA1 neurones *in vitro*. Four additional agents were studied (isoflurane, methoxyflurane, halothane and pentobarbitone) and none produced burst-like activity (table I). Instead, the major common action shared by all agents was a depression of synaptically evoked population spike amplitudes [5].

Current driven spike discharges

The reduction in population spike threshold and appearance of spontaneous population discharges in the presence of enflurane suggested that the excitability of CA1 neurones was increased by the anaesthetic. To determine if intrinsic neuronal excitability was enhanced, resting membrane potential, conductance and threshold to intracellular current injection were examined. Figure 3 shows the increase in resting membrane potential which was typically (six of seven neurones) observed following administration of enflurane. Hyperpolarization ranged from −1 to −6 mV and was concentration-dependent, with an average value of −3.1 (1.3) mV at 1 MAC.

Enflurane-induced hyperpolarizations were accompanied usually by a membrane conductance decrease, as indicated by increased voltage deflections in response to constant hyperpolarizing current pulses. Membrane conductance decreased by an average of 12 (6)% in four of six neurones in the presence of 2.0 vol% (1 MAC) enflurane. Two neurones exhibited hyperpolarization without a detectable decrease in conductance. None of the neurones studied showed either a conductance increase or depolarization.

In contrast with the increased excitability apparent in synaptically evoked population spike recordings (fig. 2), enflurane did not alter action potential generation appreciably in response to current passed through the intracellular recording electrode. Superimposed records of directly evoked action potentials in control and in the presence of enflurane are shown in figure 3. Even relatively high concentrations (e.g. 3.0 vol%) of the anaesthetic had little effect on action potential amplitude, threshold and pattern of repetitive impulse generation. The ability of hippocampal neurones to generate repetitive action potentials

TABLE I. *Comparison of anaesthetic actions on burst discharge activity, synaptic responses and excitability of hippocampal CA1 neurones. † Percent change from pre-anaesthetic control. ‡ Threshold for population spike discharge as a % change in pre-anaesthetic control (− = decrease in threshold). § References [30,31]. RMP = resting membrane potential (− = hyperpolarization); N/A = data not available. Equieffective anaesthetic concentrations were 1 MAC for enflurane (1.8 vol%), isoflurane (1.38 vol%), methoxyflurane (0.27 vol%), halothane (1.1 vol%), and pentobarbitone (100 μmol litre⁻¹)*

	Actions at equieffective anaesthetic concentrations						
	Burst activity						
Anaesthetic	*In vivo* [1–4, 20, 21]	*In vitro*	Change in EPSP† (%)	Change in PS† (%)	Change in in RMP (mV)	Change in resistance† (%)	Change in threshold‡ (%)
Enflurane	Yes	Yes	−34	−98	−6.5	+12	−28
Isoflurane	No	No	−38	−100	±1.0	+4	−24
Methoxyflurane	No	No	−29	−97	N/A	N/A	−22
Halothane	No	No	−12	−100	−3.8	−12	+10
Pentobarbitone	No	No	−17	−100	−6.2§	−17§	+14

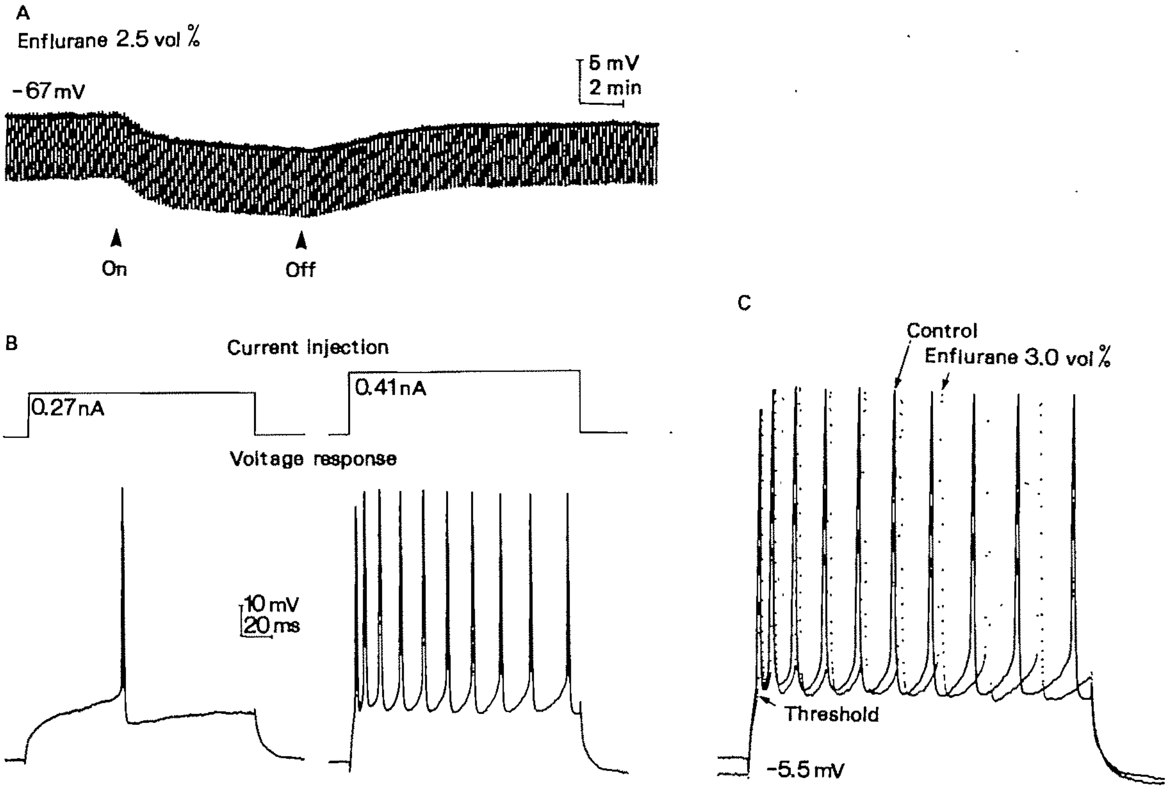

FIG. 3. A: Enflurane increased the resting membrane potential of most CA1 neurones studied. This hyperpolarization (1–6 mV) was accompanied by a decrease in conductance, measured by passing negative current (0.25 nA) pulses through the intracellular electrode. Pre-anaesthetic resting membrane potential was −67 mV; input resistance was 32 MΩ. B: Excitability of CA1 neurones was measured by injecting depolarizing current pulses sufficient to elicit a single action potential (left) or short train of spike discharges (right). Each spike was followed by an afterhyperpolarization (AHP) carried by K^+ currents. Calcium-dependent K^+ currents build up during a train of spikes and lead to a gradual slowing of discharge frequency (accommodation). C: Enflurane did not alter action potential amplitude or spike threshold, although this neurone was hyperpolarized by −5.5 mV (control resting potential was −62 mV). AHP amplitudes were slightly increased and accommodation enhanced, suggesting an enflurane-induced increase of intrinsic K^+ inhibitory currents. Note that burst discharges were not produced by direct depolarizing current stimulation in the presence of enflurane concentrations which induce synaptically evoked burst firing.

in response to maintained depolarization is limited by spike frequency accommodation, a phenomenon resulting partly from activation of potassium currents, reflected in an afterhyperpolarization following each action potential. Enflurane enhanced the rate of spike frequency accommodation (10 spikes in control *v.* nine spikes at 3.0 vol%); this was accompanied by a slight increase in post-spike afterhyperpolarization.

Thus intracellular recordings revealed no intrinsic basis for enflurane-induced increase in CA1 neurone excitability. The observed hyperpolarization and reduced ability to generate repetitive action potentials indicated that intrinsic excitability of CA1 neurones was depressed by the anaesthetic, not increased. This depression of excitability is consistent with the actions of other anaesthetics (table I) which do not induce seizure-like discharge activity, either *in vivo* [21] or *in vitro* [6, 18]. Burst discharge patterns were not observed when single CA1 neurones were stimulated by depolarizing current injection; however, the same cells displayed synaptically evoked bursts of action potentials at enflurane concentrations which produced population burst discharges in field potential recordings.

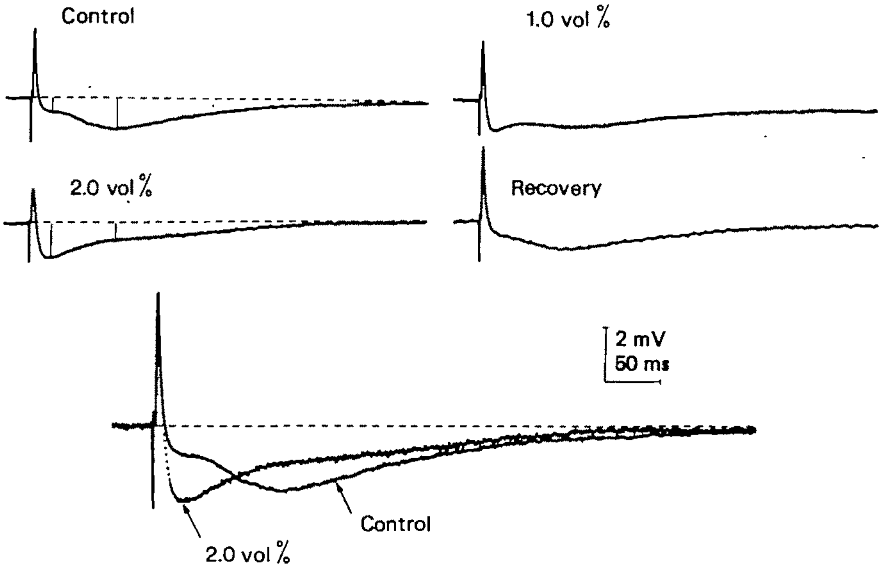

FIG. 4. Concentration-dependent effects of enflurane on synaptically evoked afterhyperpolarizations are shown in the top four records. A concentration of 2.0 vol % produced an increase in the early AHP and depressed both the late AHP and EPSP. Control and enflurane 2.0 vol % records are superimposed and enlarged in the bottom record and resting membrane potential (−67.5 mV) is indicated by the dashed line. The times of measurement of peak AHP amplitudes are shown in the top left records for both early and late AHP, 30 and 120 ms, respectively.

Excitatory and inhibitory synaptically evoked potentials

At 1 MAC, enflurane decreased the amplitudes of intracellularly recorded EPSP to approximately 30 % of control (fig. 4). Two GABA-mediated hyperpolarizing inhibitory synaptic potentials, an early and a late, follow the EPSP in response to stimulation of Schaffer collaterals [22]. At 2.0 vol % (1 MAC) enflurane depressed the late hyperpolarization to 60 % of the control value. In contrast, the early hyperpolarization was increased to more than 250 % of control; however, as the time courses of the depolarizing EPSP and the early hyperpolarization overlap, it may be that the apparent increase in the hyperpolarizing response results in part from depression of the EPSP.

NMDA block of enflurane-induced burst firing

Synaptically evoked discharge of CA1 neurones results from glutamate-induced postsynaptic depolarizations mediated by an increase in quisqualate-gated Na^+ currents and NMDA-gated Na^+/Ca^{2+} currents [23, 24]. As shown in figure 5 (left), the NMDA-mediated component of excitatory postsynaptic potentials was blocked selectively by the antagonist DL-2-amino-5-phosphonovaleric acid (APV). Concentrations from 500 nmol litre^{-1} to 20 µmol litre^{-1} produced a reversible depression (5–18 %) of synaptic responses. APV concentrations greater than 20 µmol litre^{-1} produced further depression which was not reversible. Enflurane-induced burst discharge activity was abolished totally by 5–20 µmol litre^{-1} of APV (fig. 5, right). APV did not reverse the enflurane-induced depression of synaptic responses, nor did it appear to alter facilitation of the EPSP or afterpotential amplitude.

APV at concentrations greater than 5 µmol litre^{-1} produced a marked depression (to 30–50 % of the control value at 10 µmol litre^{-1}) of population spike amplitudes, suggesting the involvement of NMDA-gated currents in depolarization–discharge coupling. Additional support for this is provided in figure 6; APV prevented both seizure-like burst discharge activity and decreases in population spike threshold normally produced by enflurane (e.g. figure 1; see also [6]). Antagonism of this enflurane effect on population spike threshold was not accompanied by a depression of paired-pulse potentiation or afterpotential amplitude (fig. 6). Concentrations of APV up to 20 µmol litre^{-1} produced only small and in-

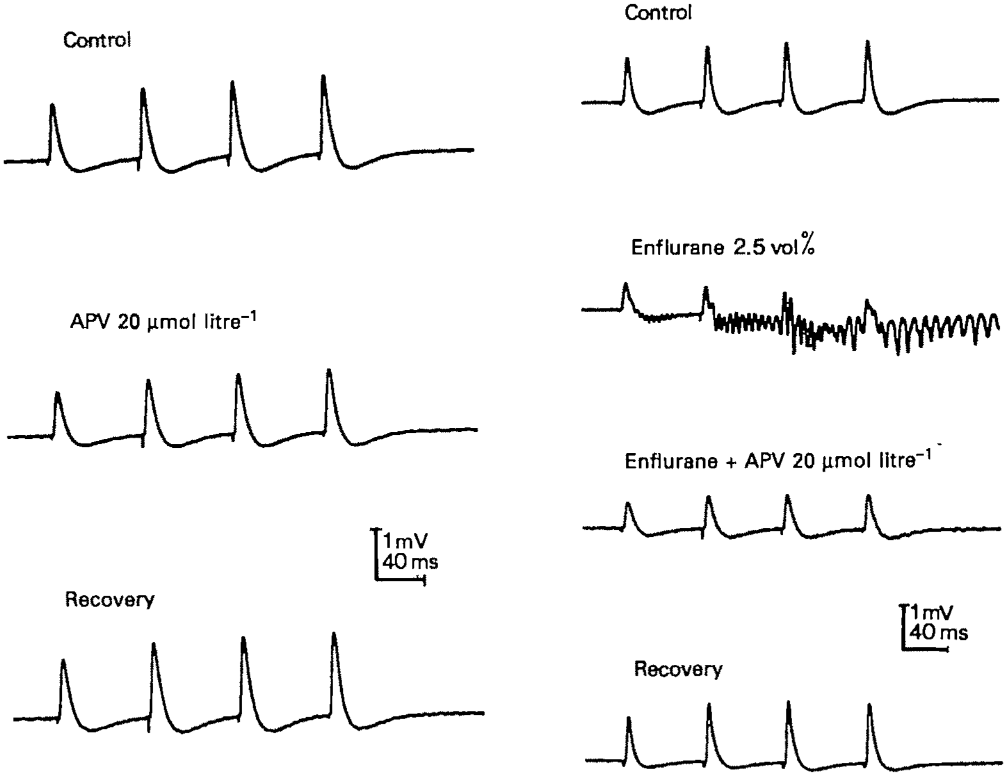

FIG. 5. Left: 2-Amino-5-phosphonovalerate (APV) depressed excitatory postsynaptic potentials (EPSP) but did not appear to alter synaptic facilitation at 8-Hz stimulus frequencies. Right: (Different preparation.) Enflurane-induced burst discharge activity was blocked by APV, although the anaesthetic-induced depression of EPSP amplitude was not altered.

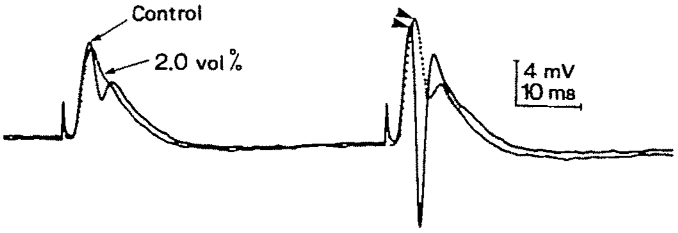

FIG. 6. Enflurane failed to elicit seizure-like discharge in the presence of APV. APV also blocked the enflurane-induced reduction of population spike threshold (arrows). Records are superimposed traces from control (——APV 10 μmol litre^{-1}) and in the presence of enflurane 2.0 vol% (.....). Paired-pulse potentiation of population spikes was not blocked by either APV or enflurane.

consistent effects on resting membrane potential (−3.0 (4.2) mV), conductance (no effect) and single neurone spike threshold response to depolarizing current (+6.2 (4.7)%). Thus the APV antagonism of enflurane-induced burst firing appears to involve selective actions at NMDA-responsive synaptic sites.

DISCUSSION

Previous studies have suggested that enflurane-induced seizure activity is associated with a combination of excitatory and depressant actions on cortical neurones [4,21]. The present study supports this view by demonstrating both depressant and excitatory actions of enflurane at the level of single hippocampal pyramidal neurones. In addition, the results suggest that enflurane produces seizure activity in a manner analogous to kainic acid and folates; that is, enflurane enhances excitatory transmission through glutamatergic synapses [13–16].

The present results also support a study [6] which indicated that depression of GABA-mediated inhibitory synaptic transmission does not contribute greatly to enflurane-induced burst discharge. In fact, enflurane enhanced the early component of the GABA-mediated afterhyperpolarization (fig. 5), which would be expected to antagonize the anaesthetic-induced hyperexcitability. A similar effect has been reported for other inhalation and i.v. anaesthetics [25–27]. It is via this same mechanism (enhanced GABA-mediated inhibition) that barbiturates, benzodiazepines and anaesthetic steroids are thought to express their anticonvulsant activities [28, 29]. Enflurane enhancement of the early component of synaptically-mediated inhibition might contribute to the anaesthetic properties of this agent, but would antagonize convulsant actions. The depression of the late inhibitory potentials produced by enflurane, on the other hand, might prolong burst discharge activity after it was initiated.

It is possible that enflurane-induced burst discharge could result from a depression of tonic GABA-mediated inhibition [30]. Depression of inhibition should result in enhanced excitability and membrane depolarization. Disinhibited neurones respond to depolarizing current injection with burst discharges [7–10]. However, the excitability of CA1 neurones was not increased (fig. 3). Burst discharges were not observed in response to current injection, and the hyperpolarization induced by enflurane suggests that any decreases in GABA-gated chloride or potassium currents are masked by opposing actions on other ion channels which contribute to the resting membrane potential.

Enflurane did not appear to depress intrinsic inhibitory currents, as post-spike afterhyperpolarization and spike frequency accommodation were not blocked. Even in the presence of relatively high concentrations of enflurane (e.g. 3.0 vol %, figure 3), current evoked discharge of CA1 pyramidal neurones was not enhanced. Instead, enflurane produced tonic hyperpolarization, decreased membrane conductance, and slowed the discharge of action potentials in CA1 neurones while increasing afterhyperpolarizations. These actions, related to effects on potassium conductance, are shared by a number of other general anaesthetics [30–33] and probably contribute to the depressant effects of these agents.

A synaptic mechanism for enflurane-induced seizure discharge

Synaptically evoked discharge of CA1 pyramidal neurones involves a complex coupling between excitatory postsynaptic potentials, spike initiation zones in the apical dendrites of these cells, and impulse generation in the soma [22]. Evidence suggests that part of this coupling process involves calcium currents regulated by glutamic acid acting on NMDA receptors [23]. As shown in figure 7, NMDA-gated calcium currents normally augment the more pronounced sodium currents which underlie excitatory postsynaptic potentials. Under certain conditions, greater stimulation of NMDA-gated calcium influx can lead to marked and prolonged enhancement of quisqualate-gated currents and, hence, result in larger excitatory postsynaptic potentials [22, 23]. In addition, calcium flow through NMDA-gated channels would stimulate voltage- and calcium-dependent currents which contribute to dendritic spike initiation [34, 35]. An increase in NMDA-gated currents probably accounts for enhanced excitatory transmission and increased efficacy of EPSP–spike coupling which has been observed in long-term potentiation at the Schaffer collateral to CA1 neurone synapse [23, 35, 36]. Overstimulation of this NMDA "system" can lead to hyperexcitability and burst discharge of CA1 pyramidal neurones [13, 14, 37].

An increase in activity at the NMDA receptor/ionophore could account for hyperexcitability associated with enflurane-induced burst discharge. Both the reduction in population spike threshold and burst discharge activity produced by enflurane may be blocked by the selective NMDA receptor antagonist APV. On the other hand, the reductions in EPSP and population spike amplitudes are not blocked by APV and probably represent separate actions of enflurane. It is not clear from the present results where enflurane acts on the glutamatergic synapse to enhance CA1 neurone excitability. Several mechanisms are possible: enflurane could enhance the tonic release of glutamate from synaptic terminals; enflurane could enhance the NMDA

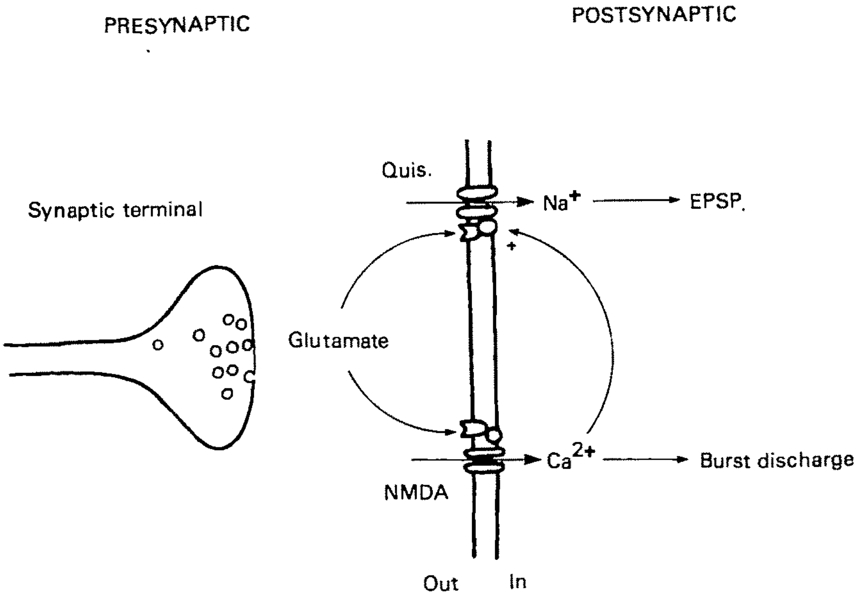

FIG. 7. Simplified diagram showing possible sites of action for enflurane-induced burst discharge at the glutamate-mediated excitatory synaptic input to CA1 pyramidal neurones. Enflurane could act to increase glutamate release from synaptic terminals, enhance current flow through N-methyl-D-aspartate (NMDA)-gated calcium channels, alter intradendritic calcium buffering, or both. Increased dendritic calcium concentrations are thought to produce burst discharge by increasing EPSP amplitudes and enhancing EPSP–spike discharge coupling [22,23,37]. Quis. = Quisqualate.

receptor or calcium ionophore activity, or both; enflurane could alter calcium buffering in CA1 neurone dendrites and thus indirectly alter the effective Ca^{2+} concentration achieved by Ca^{2+} influx through NMDA-gated channels.

In summary, the present study provides evidence for a synaptic mechanism underlying enflurane-induced burst discharge and excludes the possibility that enflurane depresses GABA-mediated and intrinsic inhibition in CA1 pyramidal neurones. Agents in clinical use which block the NMDA receptor include ketamine and dextromethorphan. It would be of interest to examine if they also inhibit enflurane-induced seizure activity.

ACKNOWLEDGEMENTS

This study was supported by NIH Grant NS13108 to J.J.K.

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Br. J. Anaesth. (1989), **63**, 306–314

EFFECTS OF PENTOBARBITONE, KETAMINE AND LIGNOCAINE ON SYNAPTIC TRANSMISSION IN THE RAT OLFACTORY CORTEX *IN VITRO*

M. IWASAKI

SUMMARY

The effects of pentobarbitone, ketamine and lignocaine on synaptic transmission in the rat olfactory cortex were studied. All agents depressed the presynaptic spike, the excitatory postsynaptic potential (EPSP) and the population spike evoked by stimulation of the lateral olfactory tract in a concentration-dependent manner. However, each anaesthetic had different effects on the processes of excitatory synaptic transmission. Pentobarbitone depressed primarily the EPSP, ketamine primarily the excitability of the presynaptic fibres and lignocaine the excitability of the presynaptic fibres; lignocaine also reduced the release of excitatory transmitters. None of the three agents influenced the passive membrane properties or the excitability of olfactory pyramidal cells. These data indicate that these agents block synaptic transmission in the olfactory cortex by different mechanisms.

Various observations suggest that general and local anaesthetics have a common mechanism of action, possibly partial block of nerve impulse conduction in the fine terminal branches of afferent axons. Sherrington and Sowton [1] demonstrated that the concentration of chloroform required to block reflex motor responses was smaller than that required to block the motor response elicited by direct stimulation of the motor nerve; consequently, it has been suggested that a possible site of action of general anaesthetics is the synapse [2–5]. However, pentobarbitone blocks the excitation of the squid giant axon and the nerve axon of lobster [6] by reducing the conductance of Na^+ and K^+ [6] in the same manner as local anaesthetics which are known to block impulse conduction along the nerve axon, although the concentrations of pentobarbitone required are high compared with those needed for general anaesthesia. The amplitude of the excitatory postsynaptic potential (EPSP) of squid giant synapse is dependent upon the amplitude of the action potential invading the presynaptic terminal [7]. Axons with small diameters are more susceptible to general anaesthetics than are larger ones [2, 8, 9]. Finally, local anaesthetics may produce general anaesthesia [10].

This study has compared the effects of pentobarbitone, ketamine and lignocaine on synaptic transmission to determine if these anaesthetics have a common or different mechanism of action.

MATERIALS AND METHODS

Male Wistar rats (180–250 g) were anaesthetized lightly with diethyl ether and killed by a blow to the back of the thorax to produce cardiac arrest [11]. The brain was removed immediately and rinsed with cold (0–5 °C) modified Krebs' solution (composition (mmol $litre^{-1}$): NaCl 126, KCl 5, KH_2PO_4 1.26, $MgSO_4$ 1.3, $CaCl_2$ 2.4, $NaHCO_3$ 26 and glucose 10). The brain was trimmed with a razor blade to a block which included the piriform cortex. This block was sliced at 450 µm perpendicularly to the surface of the olfatory cortex along the lateral olfactory tract (LOT). The slices obtained were incubated at 35 °C in Krebs' solution bubbled continuously with a mixture of 5% carbon dioxide in oxygen. After incubation for at least 90 min, each slice was placed on a plexiglas mesh in a recording chamber

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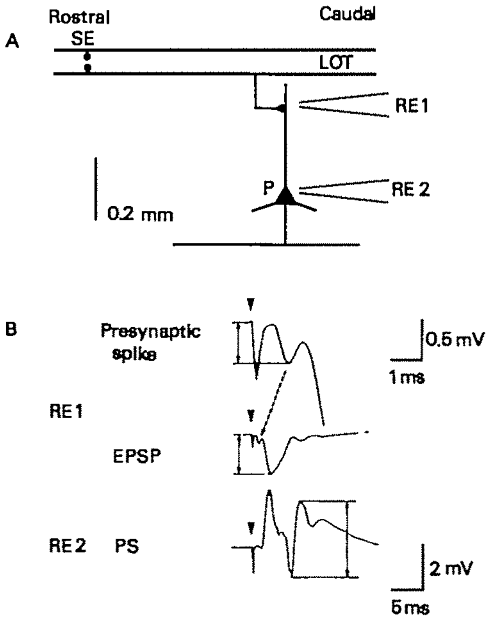

FIG. 1. A: Schematic diagram of an olfactory slice showing the stimulating (SE) and recording electrodes (RE1, RE2). B: Sample recordings from the apical dendrite area (RE1) and cell body layer (RE2). Upper trace is a high gain and fast sweep recording of the middle trace. A small negative notch before a large negative excitatory postsynaptic potential (EPSP) represents a presynpatic spike. The EPSP is reversed in polarity at RE2. Arrowheads show the onset of the LOT stimulation; bars with arrows indicate the portions of recordings used to measure the presynaptic spike, the EPSP and the population spike (PS) amplitudes. Negativity is downwards. LOT = Lateral olfactory tract; P = pyramidal cell.

and covered with a nylon mesh which was fixed with two silver wires. The chamber was perfused at a flow rate of 3–4 ml min^{-1} either with the oxygenated Krebs' solution at 35 °C or with solution to which the drug was added at the desired concentration.

The slices contained apical dendrites where the LOT axons terminated, cell bodies and basal dendrites of pyramidal cells arranged vertically to the LOT (fig. 1A). A monopolar or bipolar tungsten stimulating electrode was placed on the rostral part of the LOT to activate excitatory synaptic inputs to olfactory neurones. Supramaximal square pulses of 0.05 ms duration were delivered at 0.2 Hz. Two extracellular recording electrodes were placed on the apical dendrite area near the LOT and the cell body layer of the pyramidal cells at a distance of at least 2 mm away from the stimulating electrode. A silver chloride indifferent electrode was placed in the fluid of the recording chamber. The impedances of the extracellular recording electrodes (glass micropipette filled with Krebs' solution) were 2–5 mΩ. The membrane potential and input impedance of olfactory neurones were recorded with a glass microelectrode (containing potassium acetate 2 mol litre^{-1}, 100–150 mΩ) connected to a high input impedance amplifier with a bridge circuit (Neuro Data Model 1R183).

To study the effects of anaesthetics on excitatory amino acids and γ-amino butyric acid (GABA) receptors, quisqualate, N-methyl-D-aspartate (NMDA) and GABA were applied to the apical dendrite area of the pyramidal cell iontophoretically through three barrel microelectrodes by means of a Neuro Phore Model 2 System. The three barrels contained quisqualate 10 mmol litre^{-1} in sodium chloride 150 mmol litre^{-1} (pH 7.5), NMDA 10 mmol litre^{-1} in sodium chloride 150 mmol litre^{-1} (pH 7.5) and GABA 0.5 mol litre^{-1} (pH 3.5), respectively.

Pentobarbitone (Sigma), ketamine (Ketalar, Parke Davis & Co.) and lignocaine (Sigma) were dissolved in Krebs' solution immediately before each experiment. Before measurement of evoked potential amplitudes, Krebs' solution was perfused through the recording chamber for more than 30 min to attain stable responses. All Krebs' solutions containing these agents were perfused for 30 min and then washed out with Krebs' solution for more than 30 min.

All the recording signals were amplified and stored in a PCM data recorder (SONY 501ES) for later analysis.

RESULTS

Field potentials evoked by a single pulse

Stimulation of the LOT produced a small mono- or diphasic wave (fig. 1B, presynaptic spike) with a short latency followed by a monosynaptic negative wave (fig. 1B, EPSP) recorded from the apical dendrite area (fig. 1A, RE1). As the initial wave followed high frequency stimulation (100 Hz), it represented the compound action potentials of the LOT afferent terminals. A monosynaptic positive wave superimposed by a negative–positive wave was recorded from the cell body layer (fig. 1A, RE2). This positive wave, which reversed to a negative deflection at the apical dendrite area, was identified as an extracellularly recorded monosynaptic EPSP. The negative–positive going wave reflected the syn-

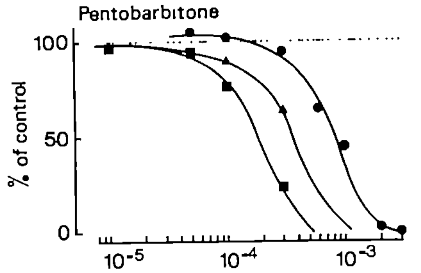

FIG. 2. Concentration–response curves of the evoked potentials after 30 min perfusion of anaesthetics. Each point indicates mean of five or six experiments.

chronous discharges of the pyramidal cells (population spike (PS)) in response to the evoked EPSP. The evidence for this interpretation of the evoked field potentials has been reviewed elsewhere [4, 11]. Ten consecutive responses were averaged with an Attack 350 (Nihon Kohden) and plotted on an X–Y plotter at a slow speed. The amplitudes were measured at the negative peak as illustrated by the arrows in figure 1B.

When each anaesthetic was applied to the bath, it depressed these three types of evoked potentials in a time- and concentration-dependent manner. Facilitatory effects [12] were not observed with any of the anaesthetics. These evoked potentials recovered completely after 0.5–2 h of washing. The order of potency of these agents on the evoked potentials was PS > EPSP > presynaptic spike (fig. 2). Pentobarbitone in concentrations less than 5×10^{-5} mol litre^{-1} did not affect any of the evoked potentials. Pentobarbitone 10^{-4} mol litre^{-1} reduced the amplitudes of the PS and EPSP by 23 % and 10 %, and 3×10^{-4} mol litre^{-1} reduced it by 76 % and 37 %. A concentration of more than 6×10^{-4} mol litre^{-1} was required to depress the presynaptic spike. Ketamine 10^{-4} mol litre^{-1} reduced the amplitudes of the PS by 16 %, but did not affect the EPSP and the presynaptic spike. The PS, the EPSP and the presynaptic spike were reduced by 70 %, 31 % and 26 % with ketamine 3×10^{-4} mol litre^{-1}, and by 100 %, 80 % and 55 % with 6×10^{-4} mol litre^{-1}, respectively. Lignocaine 10^{-5} mol litre^{-1} reduced only the amplitude of the PS, by 22 %; 5×10^{-5} mol litre^{-1} abolished the PS and reduced the EPSP and the presynaptic spike amplitudes by 53 % and 13 %, respectively, and 10^{-4} mol litre^{-1} depressed the EPSP and the presynaptic spike by 84 % and 37 %, respectively.

As shown in figure 2, there were different shifts of the concentration–response curves of these potentials for the three agents. To quantify these findings, Scholfield and Harvey [13] used the term "selectivity ratios", calculating the effective concentration for 50 % depression (EC_{50}) of each evoked potential: ratios of EC_{50} of presynaptic spike to EC_{50} of EPSP, EC_{50} of EPSP to EC_{50} of PS and EC_{50} of presynaptic spike to EC_{50} of PS. A drug with small ratios such as ketamine has a primary effect on the presynaptic spike, whereas a drug with large ratios, such as lignocaine or pentobarbitone, has selective actions on both the EPSP and the PS. The selectivity ratios are shown in table I.

TABLE I. *Selectivity ratio of the evoked field potentials*

	$\frac{ED_{50}\text{ presynaptic spike}}{ED_{50}\text{ EPSP}}$	$\frac{ED_{50}\text{ presynaptic spike}}{ED_{50}\text{ PS}}$	$\frac{ED_{50}\text{ EPSP}}{ED_{50}\text{ PS}}$
Pentobarbitone	2.3	4.6	2.0
Ketamine	1.2	1.9	1.6
Lignocaine	2.8	8.1	2.9

TABLE II. *EC_{50} (mol litre^{-1}) for the depression of the evoked field potentials. Each value was obtained from figure 2*

	Presynaptic spike	EPSP	PS
Pentobarbitone	8.2×10^{-4}	3.6×10^{-4}	1.8×10^{-4}
Ketamine	4.8×10^{-4}	3.9×10^{-4}	2.5×10^{-4}
Lignocaine	1.3×10^{-4}	4.7×10^{-5}	1.6×10^{-5}

The reduction of the PS may be derived in part from the depression of the EPSP or the presynaptic spikes, or both. To elucidate effective sites of anaesthetics, the relationship between amplitude of the evoked potentials and intensity of the LOT stimulation was examined. The concentrations used for this analysis were the EC_{50} for the PS depression (table II). Lignocaine 1.6×10^{-5} mol litre^{-1} slightly reduced the PS amplitude; thus 3×10^{-5} mol litre^{-1} was examined also. In figure 3, the presynaptic spike amplitudes were plotted against the stimulus intensities. Pentobarbitone did not affect the stimulus–response curve or the maximum amplitude of the presynaptic spike (fig. 3A). Ketamine or lignocaine slightly reduced the presynaptic spike amplitudes and decreased the slopes of the stimulus–response curves significantly (fig. 3B–D). Thus ketamine and lignocaine caused a small decrease in excitability of the LOT afferent fibres, whereas pentobarbitone had no effect.

The EPSP amplitude was plotted as a function of the presynaptic spike amplitude elicited by stimuli of varying intensity. The slope of this regression line was reduced significantly by pentobarbitone without changing the maximum amplitude of the presynaptic spike (fig. 4A). Ket-

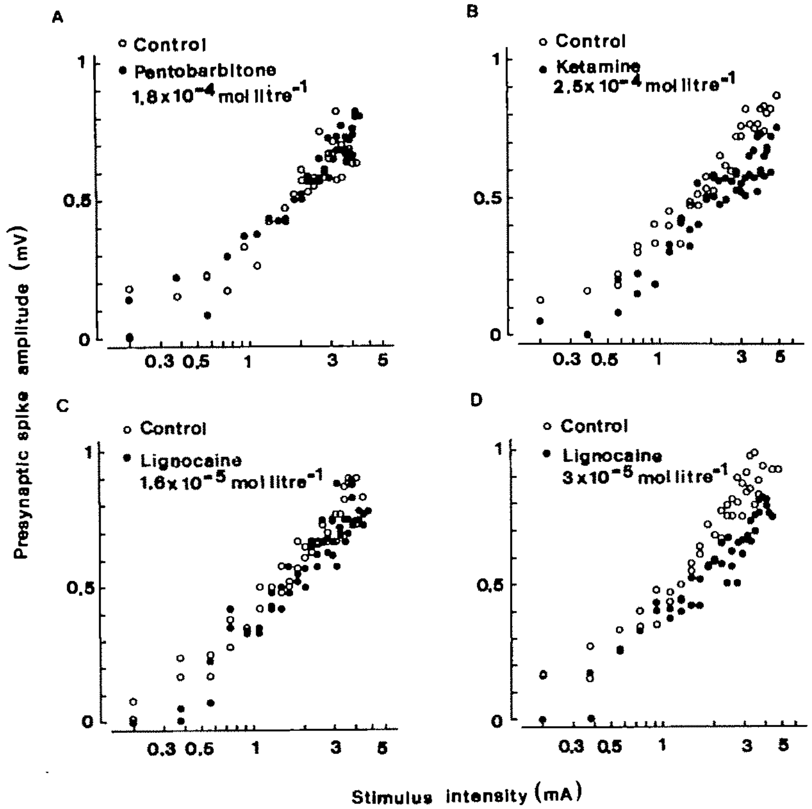

FIG. 3. Effect of anaesthetics on the excitability of the LOT afferent fibres. The amplitude of the presynaptic spike is plotted against the corresponding stimulus intensity. There is a linear relationship between the stimulus intensity and the presynaptic spike. Coefficient of the regression line was used for the statistical analysis of the slopes between control and anaesthetic solutions. A: Pentobarbitone did not affect the presynaptic spike amplitude and the slope (ns). B: Ketamine reduced the presynaptic spike amplitude and slope ($P < 0.01$). C, D: Lignocaine had an action similar to that of ketamine ($P < 0.01$). ○ = Control; ● = anaesthetic.

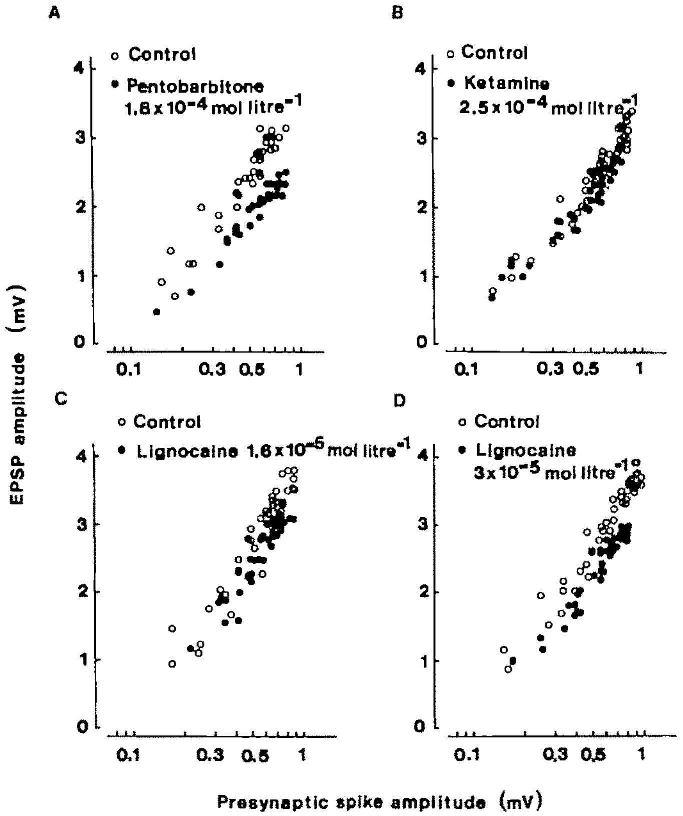

FIG. 4. Effect of anaesthetics on the EPSP in relation to the presynaptic spike. A: Pentobarbitone slightly reduced the slope of the regression line ($P < 0.05$). B: In contrast, ketamine reduced the EPSP amplitude in proportion to the decrease in the presynaptic spike amplitude and did not change the relationship between their amplitudes (ns). C, D: Lignocaine did not affect the EPSP slope (ns), but it shifted this relationship slightly to the right. ○ = Control; ● = anaesthetic.

amine reduced the EPSP amplitude in direct proportion to the reduction in presynaptic amplitude, so that the slope of the relation was not affected significantly, but the maximum amplitude of the presynaptic spike and EPSP was reduced (fig. 4B). These results indicate that pentobarbitone had a selective depressant action on the EPSP and that the depression of the EPSP by ketamine was caused by reduction in presynaptic spike amplitude. Lignocaine did not change the slope of this relationship between the presynaptic spike and the EPSP, but it caused a rightward shift (fig. 4C,D). This may result from a reduction in the amount of excitatory transmitters released from the LOT terminals, interference with the binding of transmitters to postsynaptic receptors, or both.

To determine if the three anaesthetics affect the PS, the relationship between EPSP and PS amplitude was examined. Pentobarbitone, ketamine and lignocaine reduced the maximum amplitudes of both the EPSP and the PS, but did not affect their relationship (fig. 5). Antidromic PS amplitude was not changed by relatively high concentrations (data not shown). It has been reported previously that other anaesthetics also did not affect the relationship between the amplitude of the EPSP and the PS [14]. Thus the depression of postsynaptic cell discharges resulted mostly from reduction in EPSP amplitude and not decreased electrical excitability.

Membrane potential and conductance

The resting membrane potential and conductance of olfactory pyramidal cells were measured by passing current (0.1–0.5 nA, 100 ms duration) through the recording electrode. In this experiment, the cells selected for this analysis had a

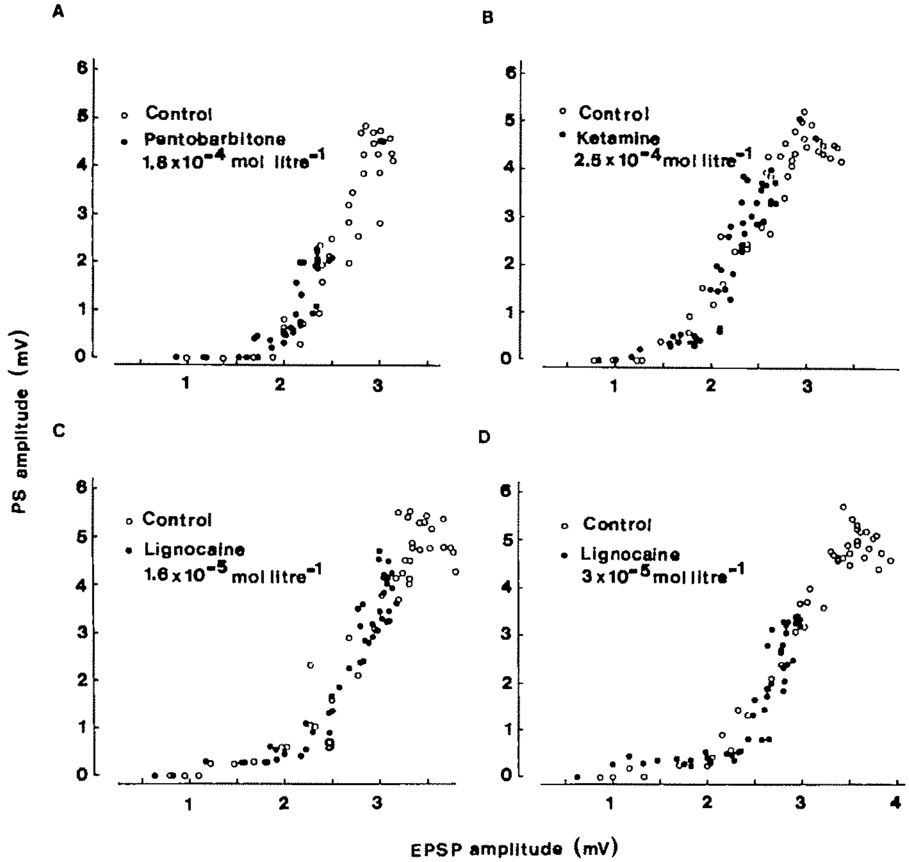

FIG. 5. Action of anaesthetics on the relation between the EPSP and PS amplitudes. ○ = Control; ● = anaesthetic. None of the three anaesthetics affected this relationship.

stable and large membrane potential (greater than −70 mV). Stimulation of the LOT generated a monosynaptic EPSP superimposed with a single spike and followed by a prolonged (100–200 ms) afterdepolarization (5–10 mV). Figure 6 shows the current–voltage relationship in the absence and presence of pentobarbitone 3×10^{-4} mol litre^{-1} (A) plotted from the electrotonic responses (B). Concentrations that markedly depressed the PS and the EPSP did not influence either the resting membrane potential or the conductance of the pyramidal cells. Similarly, lignocaine 10^{-4} mol litre^{-1} or ketamine 6×10^{-4} mol litre^{-1} (relatively high concentrations) did not affect these passive membrane properties in all the cells examined. From these findings and the field analysis in figure 5, it was demonstrated that these three agents did not affect the electrical excitability of the pyramidal cells or the electrotonic propagation of the EPSP originating from the apical dendrites to the spike generation site.

Responses to quisqualate NMDA and GABA

It is accepted that in the mammalian brain there are at least three subtypes of excitatory amino acid receptors, at which quisqualate, NMDA and kainate are relatively specific agonists, and that glutamate acts on the quisqualate receptor and aspartate on the NMDA receptor [15]. Excitatory transmitters from nerve terminals of the LOT onto the olfactory pyramidal cells are thought to be aspartate or glutamate [16, 17]. In addition, these pyramidal cells receive GABAergic terminals. Therefore, quisqualate NMDA and GABA were applied to the apical dendrite area of the pyramidal cells iontophoretically. GABA, quisqualate or NMDA depolarized the membrane of the pyramidal cells (fig. 7). The reversal

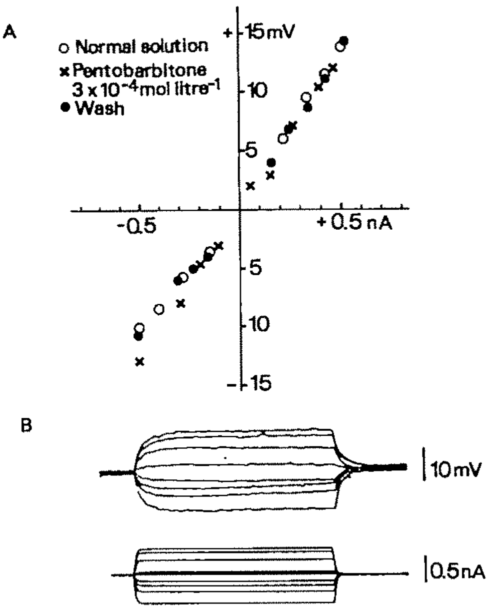

FIG. 6. Action of pentobarbitone on the current–voltage relation for a neuronal membrane in the olfactory cortex. A: Potential change plotted as a function of the applied current. The membrane conductance of this cell was not affected by pentobarbitone. The resting membrane potential remained -72 mV throughout this experiment. B: Membrane potential changes (upper) with pentobarbitone 3×10^{-4} mol litre^{-1} and applied currents (lower).

potential for GABA appeared to be higher than the resting membrane potential. The application of pentobarbitone 1.8×10^{-4} mol litre^{-1} to the bath for 8 min augmented the GABA response and reduced the quisqualate response markedly. In this particular cell, the NMDA response was reduced slightly by pentobarbitone and did not recover after washing (fig. 7A). However, in other cells, pentobarbitone did not influence the NMDA response. Lignocaine 1.6×10^{-5} mol litre^{-1} had no effect on the GABA, quisqualate and NMDA responses (fig. 7B). Ketamine 5×10^{-5} mol litre^{-1} reduced the NMDA response without affecting the GABA and quisqualate responses (fig. 7C). Ketamine 2.5×10^{-4} mol litre^{-1} also depressed the NMDA response, although it needed more than 1 h to recover to the control level.

DISCUSSION

These data suggest that pentobarbitone, ketamine and lignocaine act at different sites in blocking synaptic transmission. In this process, three evoked potentials showed different sensitivities to each anaesthetic. The use of selectivity ratios has been advocated for delineating the effects of anaesthetics on pre- and postsynaptic responses

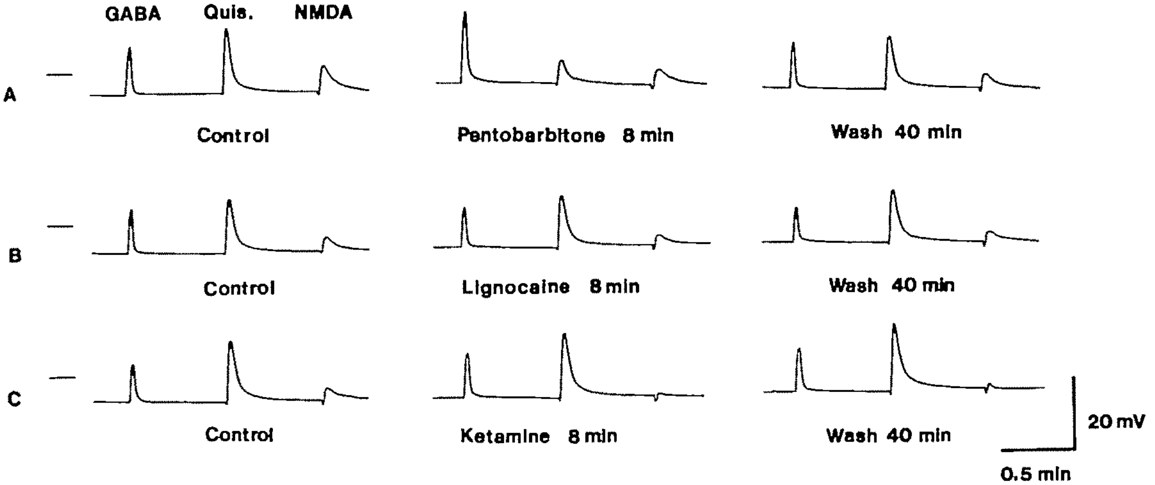

FIG. 7. Effect of anaesthetics on the response of a pyramidal neurone to iontophoretic application of GABA, quisqualate (Quis.) and N-methyl-D-aspartate (NMDA). GABA, quisqualate and NMDA were ejected onto the apical dendrite area with currents of 115 nA, 114 nA and 150 nA (1 s duration), respectively at 40-s intervals. These substances induced short-latency depolarizations. Application of pentobarbitone to the bath augmented the GABA response and reduced the quisqualate response. The NMDA response was slightly reduced during the experiment. No marked change was observed with lignocaine. Ketamine selectively depressed the NMDA response. The resting membrane potential of the pyramidal neurone was stable at approximately -78 mV throughout this experiment. Horizontal bars at left side indicate a potential of -70 mV.

[13]. Anaesthetics with large selectivity ratios, such as lignocaine or pentobarbitone, depress primarily the EPSP or the PS. Anaesthetics with small selectivity ratios, such as ketamine, depress primarily the presynaptic spike. The reduction of PS, however, may be caused by depression of the EPSP, the presynaptic spike, or both. Pentobarbitone, ketamine and lignocaine did not affect the relation between the EPSP and the PS amplitudes and the passive membrane properties (membrane potential and resistance). These findings indicate that these anaesthetics did not affect the excitability of the pyramidal cells or the electrotonic propagation of the EPSP originating from the apical dendrites to the spike initiation sites near the cell bodies in the olfactory brain slice. Thus it follows that the depression of the PS was produced by the reduction of the EPSP or the presynaptic amplitude, or both.

These three anaesthetics exhibit some characteristic features in the stimulus–response curves of these potentials. Pentobarbitone depressed the EPSP selectively without changing the electrical excitability of the presynaptic nerve as reported by Richards and Strupinski [18]. In contrast, a presynaptic action of pentobarbitone has been proposed. Weakly [19] concluded that the synaptic actions of thiopentone and pentobarbitone resulted from reduction in the amount of transmitters released from the nerve terminals. The monosynaptic spinal reflex was depressed by pentobarbitone, which reduced the presynaptic spike of the afferent nerve terminals [20]. Some anaesthetics, including pentobarbitone, modulate the release of neurotransmitters from nerve terminals [21]. It is true that high concentrations of pentobarbitone depress the presynaptic spike by a so-called local anaesthetic action, but low concentrations cause depression of the spinal reflex without affecting the presynaptic volleys [3] and depress the EPSP, but not the LOT compound action potential, in the guineapig olfactory cortex [4].

Ketamine and lignocaine reduced the maximum presynaptic spike amplitude and depressed the slope of the presynaptic spike depression curve. This suggests that both anaesthetics reduced the excitability of the LOT afferent fibres. Richards [22] showed that procaine caused a decrease in the electrical excitability of the LOT axon accompanied by slowing of impulse conduction and depression of the EPSP. In addition, lignocaine caused a rightward shift in the EPSP depression curve without affecting the slope. It is suggested that, in the present experiments, EPSP depression produced by lignocaine resulted chiefly from reduction in excitatory transmitters released from the presynaptic terminals because of ineffectiveness on the postsynaptic receptors including quisqualate.

The mechanisms of EPSP depression by pentobarbitone or lignocaine include: reduction of the amount of the excitatory transmitter release, inhibition of the binding of the transmitter with the postsynaptic receptor, and interference with the activation of Na^+, K^+ or Ca^{2+} channels induced by the excitatory transmitter. The first possibility has already been discussed. The third possibility may be excluded by ineffectiveness of anaesthetics on the passive membrane properties. The second possibility can be examined using iontophoresis. In the present study, pentobarbitone reduced the iontophoretically applied quisqualate response. A similar result has been reported with hippocampal pyramidal cells [23]. Richards and Smaje [24] observed that some anaesthetics, including pentobarbitone, depressed the sensitivity of cortical neurones to glutamate. These results suggested that the quisqualate receptor plays an important role for excitatory synaptic transmission in the rat olfactory cortex. On the other hand, ketamine selectively blocked the NMDA response. Identical results were reported using hippocampal slices [25] and somatosensory cortex [26]. Unlike the quisqualate receptor, the NMDA receptor does not have an important role in excitatory synaptic transmission in the rat olfactory system, because ketamine did not have a direct action on the depression of the EPSP. Pentobarbitone-induced GABA enhancement would potentiate recurrent inhibition [27].

In the rat olfactory slice, an excitatory effect on the PS, often seen during induction of general anaesthesia, was not observed. Similar results have been reported with pentobarbitone [4] and lignocaine [28]. In *in vivo* preparations, pentobarbitone hyperpolarized the membrane of cat hippocampal neurones [29]. These different effects between *in vitro* and *in vivo* preparations may be associated with activities of midbrain reticular formation, which controls cortical activity [30] and is affected readily by anaesthetics [31].

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Br. J. Anaesth. (1989), **63**, 315–320

INFLUENCE OF INDUCED HYPOTENSION AND SPINAL DISTRACTION ON FELINE SPINAL SOMATOSENSORY EVOKED POTENTIALS

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SUMMARY

Spinal cord injury may occur during surgical correction of spinal deformity, which is performed frequently under hypotensive anaesthesia. We have investigated the interaction between pharmacologically induced hypotension and distraction on feline spinal cord function. Twelve anaesthetized cats were subjected to hypotension (mean arterial pressure (MAP) 60 mm Hg) using a mixture of sodium nitroprusside and trimetaphan (1:5). No significant changes were observed in somatosensory evoked potentials recorded at T11. In six cats distraction was applied at L2–3 in 2.5-mm increments up to 1 cm, while MAP was maintained at 100 mm Hg (normotensive group). The remaining cats were subjected to the same distraction procedure at an MAP of 60 mm Hg (hypotensive group). In the hypotensive group, a reduction in amplitude of evoked response occurred at significantly less distraction than in the normotensive group. These data indicate that the feline spinal cord is more sensitive to spinal distraction under hypotensive conditions.

The most serious specific complication of surgical correction of scoliosis is injury to the spinal cord. The commonest mechanism of spinal cord injury during this type of surgery is probably distraction. This is most likely to occur with posterior surgical correction of the deformity, which produces a relative lengthening of the spine. Distraction injury may be produced by Harrington distraction rods [1] or by segmental spinal instrumentation with sublaminar wires [2, 3].

Controlled hypotension is advocated widely for spinal corrective surgery because of a reduction in operative blood loss and improved operating conditions [4–6]. However, animal studies have suggested that hypotension increases the sensitivity of the spinal cord to injury [7, 8] and reduces spinal cord blood flow during distraction [9]. Several case reports have implicated hypotension as a possible cause of compromised perfusion in clinical practice [10–12].

The aim of our study was to investigate the relationships between pharmacologically induced hypotension, distraction and spinal cord function measured by spinal somatosensory evoked potentials (SSEP). The feline distraction model used was similar to that described by Nordwall and colleagues [13].

MATERIALS AND METHODS

We studied 12 adult cats, mean weight 3.1 kg (range 2.5–3.5 kg) and mean length 76.7 cm (range 69–83 cm). Anaesthesia was induced with Saffan (alphaxalone and alphadolone) 1.5 ml kg^{-1} i.m. followed, after 15 min, by 1.5 ml kg^{-1} i.v. Following tracheal intubation, anaesthesia was maintained by an i.v. infusion of Saffan 1 ml kg^{-1} h^{-1} and the lungs were ventilated with nitrous oxide and 0.25–0.75 % halothane in oxygen.

The carotid artery and jugular vein were cannulated. Central venous pressure (CVP) and

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mean arterial pressure (MAP) were recorded continuously. The haematocrit and CVP were maintained at > 30% and > 4 cm H_2O, respectively, using autotransfused whole blood or Hartmann's solution. Rectal temperature was maintained at 37 °C and Pa_{CO_2} at 3.5–5.0 kPa; Pa_{CO_2} was maintained within 0.5 kPa of the initial value throughout the experiment. The inspired oxygen concentration was adjusted to maintain Pa_{O_2} > 20 kPa. Sodium bicarbonate solution was infused as required to maintain arterial pH between 7.3 and 7.4.

When required, hypotension was induced by infusing a mixture of sodium nitroprusside (SNP) 50 mg and trimetaphan (TMP) 250 mg in 500 ml of 5% dextrose solution.

A dorsal midline incision was made and fenestrations made at T11 and L5 in the ligamentum flavum and extradural recording electrodes inserted. A cutaneous ground electrode was placed at the base of the tail and a reference electrode inserted into the paraspinal muscle. Stimulating electrodes were sutured over the common peroneal nerves, which had previously been located by percutaneous stimulation. The laminae and spinous processes of L2 and L3 were exposed; the spinous processes were removed and the hooks of the distraction apparatus applied around the vertebral bodies.

A square wave direct current pulse of 0.2 ms was applied at 10 Hz to each side in turn. The smallest stimulus that produced a muscle twitch response (motor threshold) was determined. The stimulus intensity used was four times this threshold. The recording electrodes were connected to isolation amplifiers (gain 10^4, band width 8 Hz–1.6 kHz). The averaged record of 256 evoked potentials was displayed on an oscilloscope and recorded on floppy disc for later analysis. SSEP were recorded at both L5 and T11. To assess the symmetry of any changes, recordings were taken for each side sequentially.

The study consisted of two phases. Phase I examined the effect of hypotension alone on electrophysiological function in the undistracted cord (12 cats). In phase II, which followed immediately, six cats underwent normotensive distraction (group A), and six cats underwent hypotensive distraction (group B).

Phase I

MAP was stabilized at 100 mm Hg by adjusting the inspired halothane concentration at 0.25–0.75%. Four sets of control SSEP were recorded. Hypotension was induced and maintained at MAP 60 mm Hg for 30 min; SSEP recordings were taken at 5, 10, 20 and 30 min.

Phase II

In group A, MAP was restored to 100 mm Hg by discontinuing the infusion of hypotensive drugs. After a period of stabilization, two SSEP recordings were made (zero distraction). Distraction (measured at the facet joints using calipers) was applied in 2.5-mm increments up to 1 cm. After 2.5 and 5 mm of distraction, SSEP were recorded at 0 and 5 min. After 7.5 and 10 mm of distraction, SSEP were recorded at 0, 5, 10, 20 and 30 min. Distraction was then released and further SSEP recorded at 10, 20 and 30 min.

In group B, MAP was maintained at 60 mm Hg and distraction applied in the same manner as in group A.

Data were analysed by paired and unpaired Student's *t* tests and analysis of variance for repeated measures. Differences were considered significant when $P < 0.05$.

RESULTS

There was no significant difference in physiological variables between the groups (table I).

TABLE I. *Physiological variables (mean (SD))*

Phase I	Normotensive (Control)	Hypotensive (60 min)
Pa_{O_2} (kPa)	28 (5)	25 (3)
Pa_{CO_2} (kPa)	4.4 (0.4)	4.1 (0.5)
Hct (%)	35 (4)	34 (4)
CVP (mm Hg)	5.5 (2.1)	5.8 (1.8)
Phase II	**Before distraction**	**After distraction**
Group A		
Pa_{O_2} (kPa)	26 (2)	25 (2)
Pa_{CO_2} (kPa)	4.0 (0.3)	4.3 (0.3)
Hct (%)	32 (4)	31 (5)
CVP (mm Hg)	4.3 (1.6)	4.5 (1.3)
Weight (kg)	3.2 (2.5–3.5)	
Length (cm)	77 (83–71)	
Group B		
Pa_{O_2} (kPa)	26 (2)	23 (3)
Pa_{CO_2} (kPa)	4.2 (0.3)	4.6 (0.4)
Hct (%)	34 (4)	35 (3)
CVP (mm Hg)	5.8 (1.3)	5.3 (1.6)
Weight (kg)	3.0 (2.5–3.5)	
Length (cm)	75 (82–69)	

A dose of 1.5–12 ml h^{-1} of the SNP–TMP mixture was required to maintain hypotension.

Control SSEP

Figure 1 shows a typical SSEP trace. There was no significant difference in control SSEP amplitude between groups A and B, or between sides. Consequently, the results from both sides were pooled for further analysis.

Phase I

There were no significant changes in P1–N1 amplitude, or P1, N1 and P2 latencies during hypotension without distraction (table II).

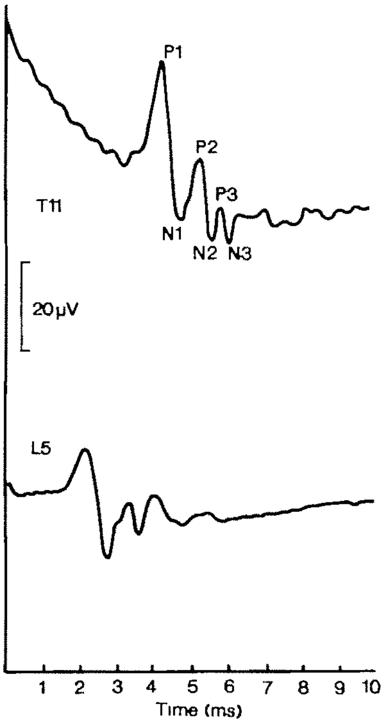

FIG. 1. Typical SSEP recording. The upper trace was recorded at T11 and the lower trace at L5. Latency is measured from time of stimulus until the first two positive peaks (P1 and P2) and the first negative peak (N1). Amplitude is measured from P1 to P2.

Phase II

All group A animals tolerated distraction up to 10 mm for 20 min without change in SSEP.

In all group B animals, changes occurred in the T11 evoked response before 10 mm of distraction had been applied for 20 min. In one animal the SSEP changed after 5 min at 2.5 mm of distraction.

Amplitude change

A significant difference in P1–N1 amplitude was found between the groups for a distraction greater than 5.0 mm for 5 min (fig. 2). The amplitude decreased first by 50% of control on the right side in three cats, on the left side two cats, and was simultaneous in one cat.

Latency change

As the control latencies in group A (4.7 (SD 0.4) ms) were significantly different from those of group B (4.1 (0.4) ms), latency changes were analysed as an increase or decrease from control values (fig. 3). An increase in the latency to P1 was part of the major change in SSEP produced by distraction, but in no case did this precede a decrease in amplitude. The change in latency was relatively small compared with the difference between animals. There was no consistent pattern of loss of the later peaks of the evoked potential.

Change with time

In group A, distraction was released on completion of the study and further SSEP were recorded at 10, 20 and 30 min. No significant differences were seen between these recordings and those taken at the beginning of the experiment.

Change in the SSEP recorded at L5

Some variation in P1–N1 amplitude recorded at L5 was observed concurrently with amplitude changes at T11 during hypotensive distraction. In

TABLE II. *Mean (SD) effect of hypotension on SSEP* (n = *24*). † *ANOVA for repeat measures*

	MAP (mm Hg)					
	100	60				
	0 min	5 min	10 min	20 min	30 min	†*P*
P1–N1 AMP (µV)	35.9 (10.0)	36.0 (9.0)	35.3 (9.9)	34.0 (9.5)	33.2 (9.2)	> 0.4
P1 Latency (ms)	4.4 (0.5)	4.3 (0.6)	4.4 (0.6)	4.4 (0.6)	4.4 (0.6)	> 0.2
N1 Latency (ms)	5.0 (0.6)	5.0 (0.6)	5.0 (0.6)	5.0 (0.7)	5.0 (0.6)	> 0.3
P2 Latency (ms)	5.4 (0.6)	5.4 (0.7)	5.4 (0.7)	5.3 (0.7)	5.3 (0.7)	> 0.16

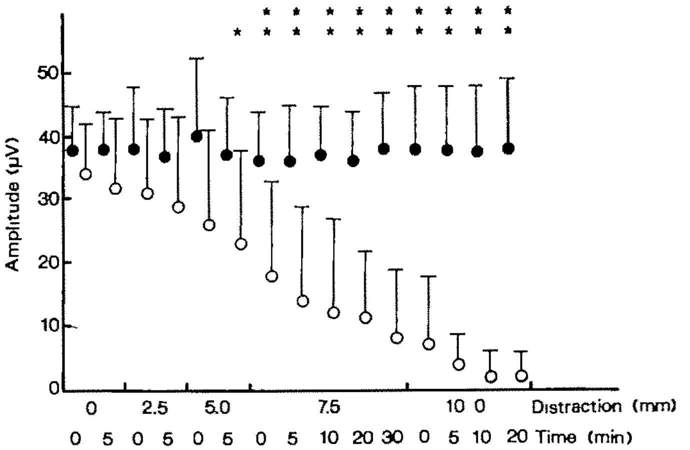

FIG. 2. Change in mean amplitude during the distraction routine (phase II). ● = Group A (MAP 100 mm Hg); ○ = group B (MAP 60 mm Hg). Bars indicate one SD.

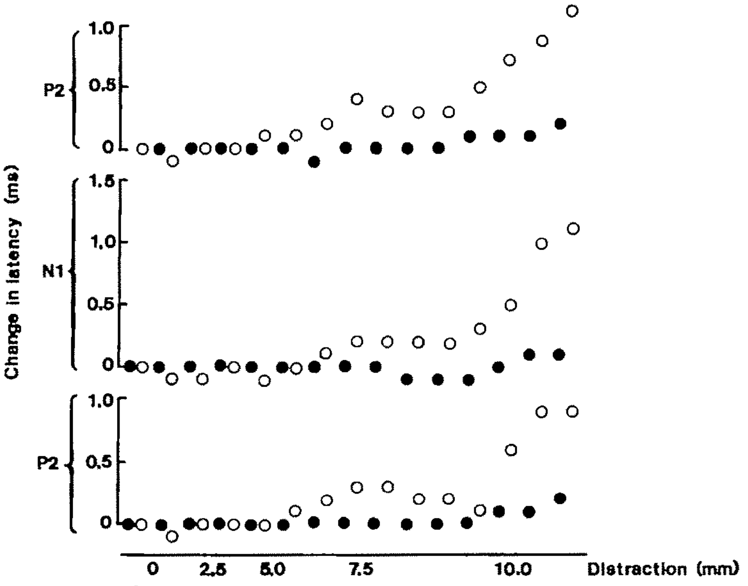

FIG. 3. Mean change in latency during the distraction routine (phase II). ● = Group A (MAP 100 mm Hg); ○ = group B (MAP 60 mm Hg).

two subjects, a marked increase was observed, and in one a small reduction was seen.

DISCUSSION

Our results show that the feline spinal cord was more sensitive to distraction under hypotensive than normotensive conditions, while hypotension to a similar degree without distraction produced no change in SSEP. It is probable that ischaemia is the main mechanism of injury during distraction [9]. Electrophysiological activity in the long tracts is relatively resistant to reduced blood flow, but is disturbed when white matter flow decreases to less than 30% of normal [14]. Using a similar distraction model in cats, Nordwall and colleagues [13] found that changes in the SSEP correlated with change in motor function of the lower limbs. Dolan and colleagues [9], found that spinal cord blood flow (SCBF) was reduced in the distracted segment of cord and SSEP changes were associated with a 72% reduction in white matter SCBF. Both groups found that these changes occurred when the distraction exceeded 1.5 cm in the normotensive cord. Preliminary investigations in our laboratory showed that changes in SSEP at normotension occurred with interfacetal distances greater than 1.25 cm, while most changes during hypotension occurred at 0.75–1.0 cm, but in some cases more than 20 min elapsed before changes became evident (Crawshaw, Yeoman and Bradshaw, British Scoliosis Society 1984). We therefore elected to use a distraction regimen slightly different from that used by the Nordwall and Dolan groups [9, 13]. In the normotensive 3-kg cat, distraction of more than 1.0 cm for 20 min was tolerated without change in the SSEP.

Investigations [15–17] into the effect of hypotension on cord blood flow in dogs (MAP 50–60 mm Hg) have shown a difference between SNP and TMP. While cord blood flow was maintained well with SNP, a 50% reduction occurred with TMP. In the present study we used a mixture of these two agents and it is possible that SCBF could have been reduced, although remaining sufficient to maintain electrophysiological function, provided that an additional distractive insult was not applied. Kling and co-workers [16, 17] found no reduction in SCBF when distraction (2 cm) was applied over 10 segments under hypotensive conditions in a dog model. In humans, multisegmental distraction of 2 cm may occur during scoliosis correction. With traumatic deformities a distraction of 1 cm over one intervertebral space is possible. In this study the minimum distraction that produced a marked SSEP change was 2.5 mm.

No significant SSEP changes were seen in group A throughout the experimental period; thus the changes in group B were not a result of temporal effects. When changes were seen, there was no consistent pattern with respect to the different components of the evoked response. We found that the P1–N1 amplitude was the most reliable indicator of significant evoked response changes. In animal experiments Aki and Toya [18] found that amplitude changed before latency. Tamaki and colleagues [19] found amplitude change was the most valuable clinical parameter.

An increase in latency to the first peak of the SSEP was always part of the change in the evoked response. Unfortunately, these latency changes were often small and never preceded the amplitude change. Changes in the shape of the lesser peaks of the evoked response were not a reliable sign of significant SSEP change.

In the majority of cases, SSEP change with distraction was not symmetrical; changes on one side preceded the other. Unilateral changes have been reported clinically [20] and emphasize the importance of bilateral SSEP monitoring.

Changes in SSEP recorded at L5 indicate that electrophysiology is disturbed at some distance caudal to the level of distraction. Spinal cord blood flow is reduced over several segments on each side of the distraction level [9]. Although this might be expected to produce a reduction in SSEP amplitude, increases in SSEP and electrospinogram amplitudes have been reported caudal to compressive lesions [21], possibly because of release from inhibitory influence.

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Br. J. Anaesth. (1989), **63**, 321–325

INTERACTIONS BETWEEN DILTIAZEM AND INHALATION ANAESTHETICS IN THE ISOLATED HEART

M. D. CARCELES, F. S. MIRALLES, M. L. LAORDEN AND J. HERNANDEZ

SUMMARY

It has been postulated that inhalation anaesthetics may interfere with calcium movement across cell membranes. We have evaluated the interaction between diltiazem and the inhalation anaesthetics halothane and isoflurane on sinus automaticity in the isolated right atrium (SAIRA). Isoflurane significantly reduced atrial rate at all concentrations tested. However, halothane produced only a small but significant decrease at the higher concentrations used (1–2 v/v%). Diltiazem modified the maximal negative chronotropic response to inhalation anaesthetics. Maximum depression of SAIRA was significantly greater in the presence of two different doses of diltiazem compared with exposure to halothane and isoflurane alone. These results suggest that inhalation anaesthetics may block the influx of extracellular calcium through voltage-dependent calcium channels inhibited by diltiazem.

Although the mechanisms underlying the cardiac effects of inhalation anaesthetics are not understood completely, they appear to be related to changes in ionic fluxes, principally those involving calcium [1]. There is also evidence for a similarity between the pharmacological effects of anaesthetics and calcium channel blockers. Indeed, depressant effects on sino–atrial node conduction produced by halothane, enflurane and isoflurane have been shown to be similar to those of the cardioactive calcium blockers [2].

The aim of the present study was to examine the interaction between different doses of diltiazem and the inhalation anaesthetics halothane and isoflurane on sinus automaticity in isolated right atria (SAIRA), in which the actions of extracardiac systems are eliminated.

MATERIALS AND METHODS

Experiments were carried out on isolated right atria preparations. Sixty-six male Sprague–Dawley rats (weights 150–200 g) were humanely killed. The chest was opened by midsternal incision and the right atrium was isolated by a technique similar to that described previously [3, 4]. The right atrium was suspended in a 30-ml organ bath (Allihn tube) with 0.5 g of resting tension. Tyrode solution was used (composition (mmol litre^{-1}): NaCl 136.9; KCl 5.0; $MgCl_2$ 1.05; $CaCl_2$ 1.8; NaH_2PO_4 0.4; $NaHCO_3$ 11.9; dextrose 5). The bathing solution was maintained at 37 °C, pH 7.4 and bubbled with 5% carbon dioxide in oxygen. The frequency of spontaneous contraction of the right atrium was measured using a force–displacement transducer (Grass FT 03) and recorded on a Dynograph Beckman polygraph.

After a 30-min stabilization period, cumulative concentration–response curves to halothane (I.C.I.) and isoflurane (Abbott) (concentration range 0.1–2 v/v%) were obtained. Both volatile anaesthetics were delivered from standard vaporizers (Ohmeda) which were calibrated with the EMMA multigas analyser (Engström), itself previously calibrated against certified gas mixtures. Similar dose–response curves for halothane and isoflurane were obtained in the presence of

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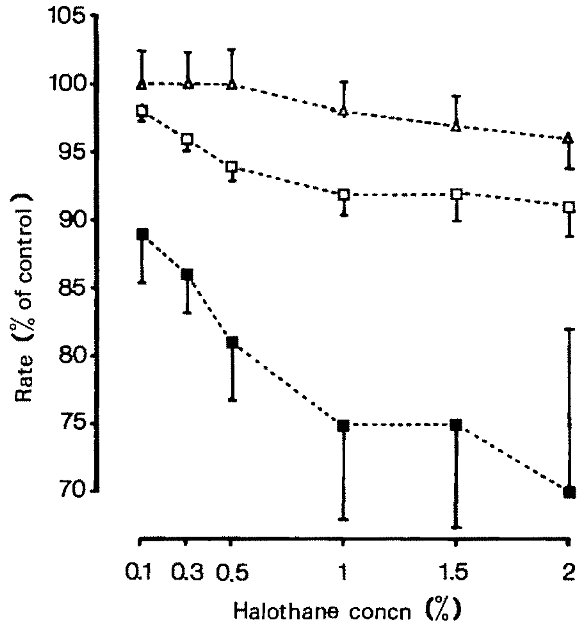

FIG. 1. Effect of halothane on atrial automaticity in the absence (△, $n = 10$) and in the presence of diltiazem (5×10^{-7} mol litre^{-1} □, $n = 6$ and 1×10^{-6} mol litre^{-1} ■, $n = 6$) (mean, SEM).

diltiazem (Esteve Laboratories) 5×10^{-7} and 1×10^{-6} mol litre^{-1} added to the organ bath in normal saline 0.1 ml 5 min before halothane or isoflurane. Results for inhalation anaesthetics alone are expressed as percent changes from baseline values without diltiazem. Results with inhalation anaesthetics in the presence of diltiazem are expressed as percent changes from the baseline values after diltiazem. In order to compare the inhibitory effect of the agent used in absence and in presence of two different doses of diltiazem, we measured the corresponding IC_{50} (the dose of which produced a 50% decrease of atrial rate) for each set of experiments [5].

Data were analysed by Student's t test and analysis of variance. An analysis of linear regression with the log of response was used for the estimation of IC_{50}. $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Effects of halothane

The concentration–response curves for halothane in the absence and presence of two different concentrations of diltiazem are illustrated in figure 1. The smaller concentration of diltiazem (5×10^{-7} mol litre^{-1}) was devoid of any effect on the atrial rate. However, diltiazem 1×10^{-6} mol litre^{-1} produced a small (13%) but significant decrease of SAIRA. Halothane alone did not change SAIRA at low concentrations (0.1–0.5 v/v%), but it produced a small (4% maximal), significant decrease at the higher concentrations (1–2 v/v%). Diltiazem modified the maximal negative chronotropic response to halothane. The maximal decrease in SAIRA induced by halothane (2 v/v%) alone was to 96 (SEM 2.2)% of control. In the presence of diltiazem 5×10^{-7} and 1×10^{-6} mol litre^{-1}, the maximal decrease of atrial rate was to 91 (2.3)% and 70 (8.5)%, respectively. The difference between each of these two values and the maximal decrease in SAIRA induced by halothane was significant (table I).

Effects of isoflurane

The concentration–response curve for isoflurane in the absence and presence of two different concentrations of diltiazem is shown in figure 2. The results obtained with diltiazem alone were similar to those described previously. SAIRA was significantly depressed from control values by all concentrations of isoflurane. The

TABLE I. *Effects of diltiazem on the maximal negative chronotropic response to halothane and isoflurane (mean (SEM)). IA = Inhalation anaesthetic.* n = *6 for each group except for halothane and isoflurane alone* (n = *10*)

	Halothane			Isoflurane		
	Maximal effect (%)	Change (%)	P	Maximal effect (%)	Change (%)	P
IA alone	91 (2.2)	—	—	91 (1.8)	—	—
With diltiazem						
5×10^{-7} mol litre^{-1}	91 (2.3)	5	< 0.05	84 (2.4)	7	< 0.05
1×10^{-6} mol litre^{-1}	70 (8.5)	26	< 0.001	84 (2.1)	7	< 0.05

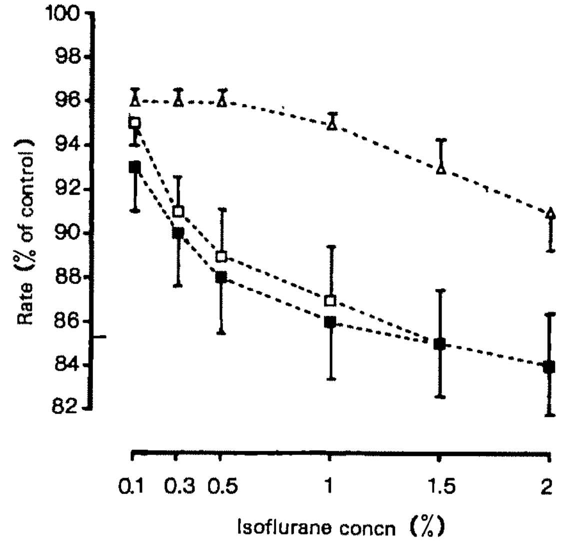

FIG. 2. Effect of isoflurane on atrial automaticity in the absence (△, $n = 10$) and in the presence of diltiazem (5×10^{-7} mol litre^{-1} □, $n = 6$ and 1×10^{-6} mol litre^{-1} ■, $n = 6$) (mean, SEM).

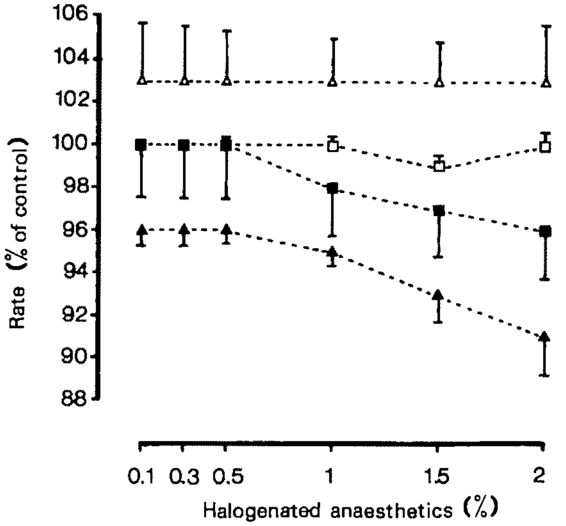

FIG. 3. Effect of halothane (■, $n = 10$) and isoflurane (▲, $n = 10$) on atrial automaticity in normal calcium solution compared with the effect of halothane (□, $n = 6$) and isoflurane (△, $n = 6$) in an increased concentration of calcium (mean, SEM).

maximal decrease (to 91 (1.8)% of control) was obtained at the higher concentration (2 v/v%) (table I). When diltiazem was present in the organ bath, isoflurane (2 v/v%) produced a maximal decrease of control SAIRA of approximately 16%, significantly greater than that produced by isoflurane alone (9%).

The IC_{50} values of halothane and isoflurane with and without the two doses of diltiazem are summarized in table II. The difference in IC_{50} between halothane alone and in the presence of diltiazem was significant ($P < 0.02$). Similarly, the IC_{50} of isoflurane alone was significantly greater than that in the presence of the two doses of diltiazem ($P < 0.001$).

Calcium

Concentration–response curves to halothane and isoflurane were also obtained in the presence of a high concentration of calcium (5.4 mol litre^{-1}) (fig. 3). The calcium concentration attenuated the inhibitory effects of high concentrations of halothane and isoflurane, but the attenuation was not statistically significant.

DISCUSSION

This study was designed to examine the interaction between inhalation anaesthetics and diltiazem on isolated right atria which were free from the compensating mechanisms present in intact animals or man. This method has been used widely to evaluate the actions and interactions between different drugs on chronotropic automaticity [3,4,6].

Our results confirmed the findings of other investigators [2]: halothane and isoflurane alone showed depressant effects on atrial automaticity

TABLE II. *IC_{50} of the inhalation anaesthetics halothane and isoflurane in the absence and presence of diltiazem upon sinus automaticity of isolated right atria (mean (SEM)). IA = Inhalation anaesthetic.* n = *6 for each group except for halothane and isoflurane alone* (n = *10*)

	Halothane	P	Isoflurane	P
IA alone	1.41 (0.14)	—	1.85 (0.16)	—
With diltiazem				
5×10^{-7} mol litre^{-1}	1.00 (0.1)	< 0.02	0.83 (0.11)	< 0.001
1×10^{-7} mol litre^{-1}	1.00 (0.13)	< 0.02	0.87 (0.11)	< 0.001

similar to those of the cardioactive calcium blockers. It had been suggested from *in vivo* experiments that the depression of cardiac muscle function by halothane appeared to be antagonized by calcium [7,8]. In the present *in vitro* model, the negative chronotropic effects induced by halothane and isoflurane were sensitive to changes in the concentration of calcium in the medium. It has been established that the myocardial depression produced by inhalation anaesthetics is related, at least in part, to alterations in calcium ion flux [1,9]. The importance of calcium as a carrier of the inward current of the sinus node is shown by the observation that an increase in Ca^{2+} concentration increases the sinus rate [2]. In addition, calcium antagonists suppress sinus node activity by decreasing the rate of phase 4 and phase 0 depolarization and the amplitude of the action potential [10].

The pharmacological interactions between inhalation anaesthetics and calcium channel blocking drugs *in vitro* [11, 12], *in vivo* [13–15] and in humans [16, 17] have been described previously. The data obtained from *in vitro* experiments showed that calcium channel blockers modified the negative inotropic effects induced by inhalation anaesthetics, but the effects on cardiac chronotropism have not been reported. Our results using isolated right atria showed that halothane dose–response curves obtained in the presence of the two different concentrations of diltiazem were significantly more inhibitory. Similar results were obtained with isoflurane, but the chronotropic effects it induced in the presence of diltiazem were less than those seen with halothane. These data are in agreement with those of Lynch [18], who demonstrated that halothane appeared to have calcium channel blocking activity, while isoflurane appeared to affect intracellular calcium kinetics [19].

Although diltiazem and halothane or isoflurane are considered to have minimal adverse effects on heart rate, our results demonstrated that halothane and isoflurane exerted a direct negative chronotropic effect on SAIRA. These inhibitory effects induced by both agents were blocked in the presence of increased calcium concentration in the organ bath, but not significantly. The maximal decrease in SAIRA induced by inhalation anaesthetics was significantly greater in the presence of increasing concentrations of diltiazem. At present, there is no evidence that the patient receiving calcium channel blocking drugs, without other complicating factors, presents a significantly increased risk for anaesthesia and surgery. However, these observations may have some clinical relevance to patients concurrently receiving the calcium antagonist, diltiazem, and submitted to general anaesthesia.

ACKNOWLEDGEMENT

The authors are grateful to Matilde Campos (Department of Statistics, School of Medicine, Murcia, Spain) for statistical advice.

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Br. J. Anaesth. (1989), **63**, 326–329

ULTRASONOGRAPHIC STUDY OF THE SPREAD OF LOCAL ANAESTHETIC DURING AXILLARY BRACHIAL PLEXUS BLOCK

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SUMMARY

Ultrasonography has been used to demonstrate the anatomy of the axilla, to confirm the placement of a cannula and to visualize the spread of a local anaesthetic solution in the axillary sheath of 10 patients (aged 17–70 yr) for surgery of the forearm and hand. The block was successful in all subjects.

Methods used to demonstrate the spread of solutions in the axillary sheath include the use of radio-opaque dyes and x-rays [1] and cadaveric studies which involved dissection after injection of self-hardening solutions [2]. Ultrasonography has been used to measure the depth to the extradural space [3] and to locate the internal jugular vein [4]. In this study, ultrasonography was used to show sections of the axilla, to confirm the position of a cannula in the "axillary sheath" and to visualize the spread of an aqueous solution of local anaesthetic. The axilla was chosen because it allowed comparison of our observations with previous studies.

PATIENTS AND METHODS

We studied 10 patients (aged 17–70 yr, ASA I) who presented for surgery of the forearm and hand. A modification of the technique described by Sada, Kobayoshi and Marakami [5] was used, with the patient placed supine with the arm abducted 70°, the shoulder externally rotated and elbow flexed at 90°. The axillary artery was palpated high in the axilla and a 21-gauge polypropylene cannula with an inner metal needle was inserted under local anaesthesia. The cannula was directed towards and superior to the point of maximal pulsation until a click was felt. The cannula was then advanced over the metal needle until resistance was felt. No attempt was made to elicit paraesthesiae. Correct positioning of the cannula was confirmed by ultrasonography using a Toshiba SAL 38 B with a TP8300 thermal printer and a linear 64 element electronically-scanned probe operating at 3.5 MHz. The anatomy of the axilla was recorded 90° to the axis of the axillary vessels above, at and below the level of the pectoralis minor muscle before and after injection of 1.5 % lignocaine 30 ml with adrenaline 1:200000. The time to onset of block suitable for surgery was measured from the time of injection.

RESULTS

Paraesthesiae were not produced and the axillary vessels were not punctured in any patient. Successful block was achieved in all. All patients required a tourniquet for the surgery, but only two complained of mild discomfort from the tourniquet, which was relieved with fentanyl 50 µg and droperidol 2.5 mg i.v. Two patients had an incomplete sensory block over the deltoid. All the other patients had a complete block of the axillary nerves derived from C5 to T1. One patient required diazepam 5 mg for anxiety. Onset time was 18 min (mean; range 8–35 min). All patients were monitored after operation until total regression of motor block, which occurred within 2.5 h.

Figure 1 shows the anatomy of the axilla. The thick lines on the line drawing show the ultrasound sections in relation to the anatomy of the axilla. The left upper picture shows the section

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Accepted for Publication: February 20, 1989.

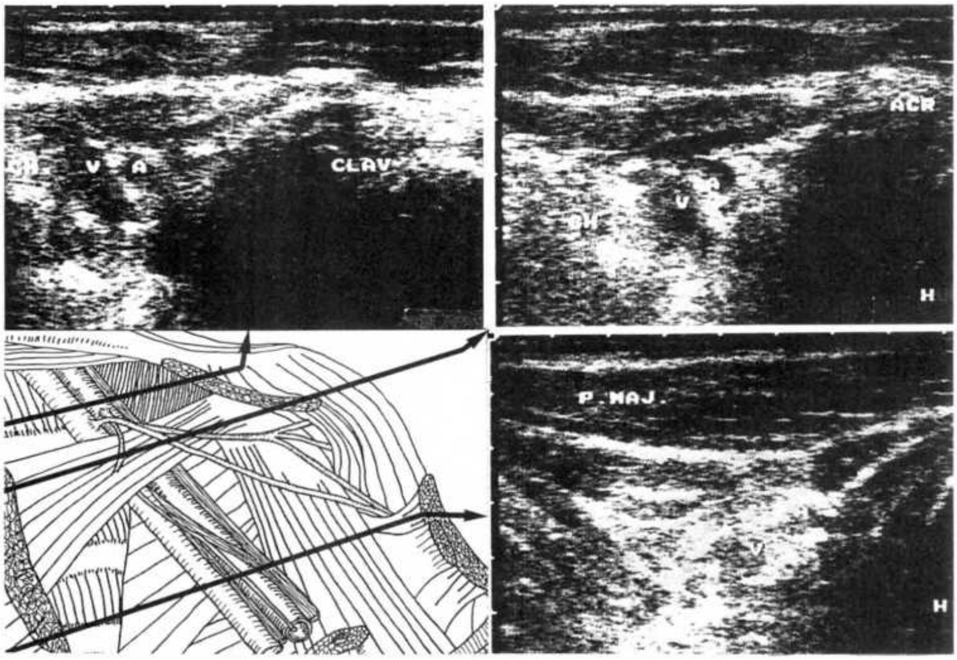

FIG. 1. Anatomy of the axilla. V = vein; A = artery; CH = chest wall; CLAV = clavicle; ACR = attachment to coracoid process; P.MAJ. = pectoralis major muscle; H = humerus.

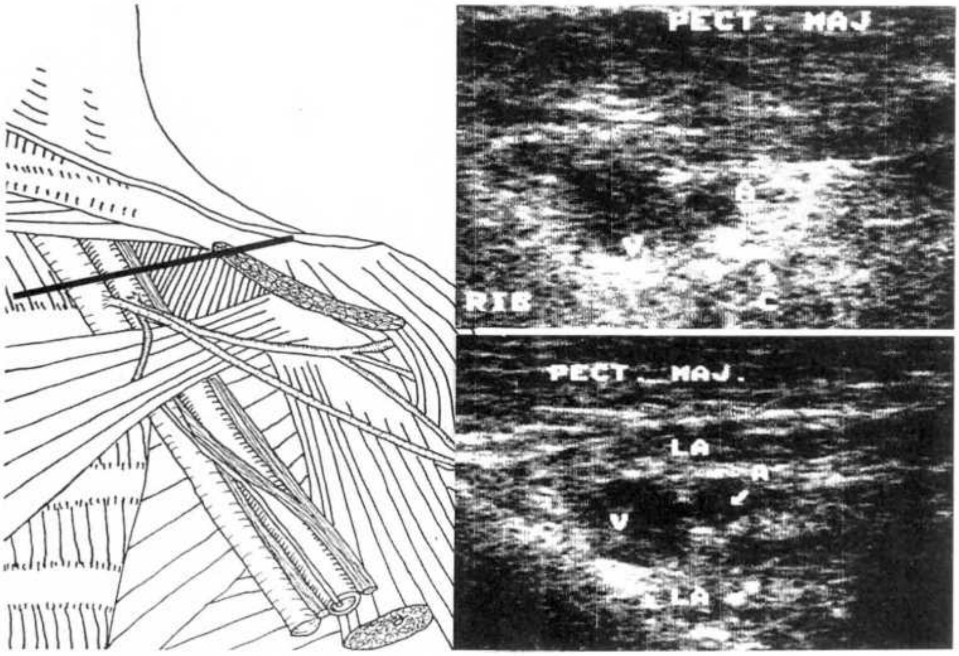

FIG. 2. Section across the apex of the axilla showing the artery (A) and vein (V) before (upper ultrasound picture) and after (lower ultrasound picture) the injection of 30 ml of 1.5% lignocaine solution in water (LA). The artery and vein are better defined after LA injection, but are not separated. PECT.MAJ. = pectoralis major.

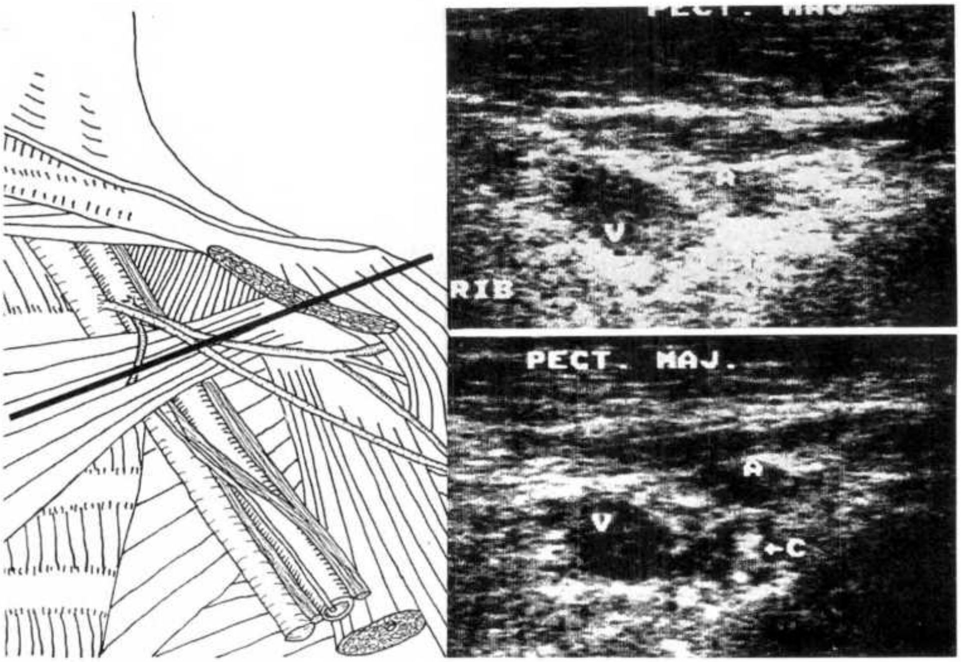

FIG. 3. Section of the mid-axilla before (upper ultrasound picture) and after (lower ultrasound picture) injection of 30 ml of 1.5% lignocaine in water. The thoraco–acromial branch of the axillary artery is clearly seen. The artery (A) and vein (V) appear separated after injection of local anaesthetic through the cannula (C).

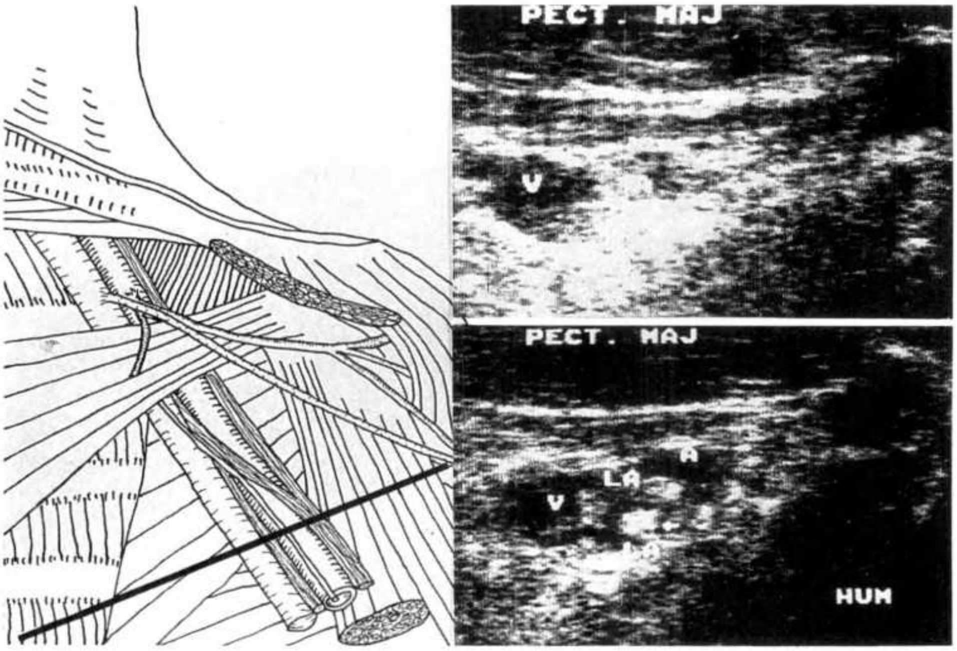

FIG. 4. Section across the base of the axilla before (upper ultrasound picture) and after (lower ultrasound picture) injection of 30 ml of 1.5% lignocaine solution in water. The artery (A) and vein (V) appear separated after the injection of local anaesthetic solution (LA) and the plastic cannula is visible (←).

through the apex of the axilla, where the artery and vein lie close to the chest wall. The cephalic vein may be seen entering the axillary vein after piercing the clavi–pectoral fascia. The right upper picture shows the mid-axilla. The attachment of the pectoralis minor muscle to the coracoid process and the thoraco–acromial branch of the axillary artery are seen. The humeral head appears as a dark area at the right lower corner of the picture. The right lower picture shows the section through the base of the axilla. The coraco–brachialis and biceps muscles may be seen beneath the pectoralis muscle. The musculo–cutaneous nerve (between the small black arrows) may be seen running in the coraco–brachialis muscle.

Figures 2–4 show the apex, middle and base of the base of the axilla before (upper ultrasound picture) and after (lower ultrasound picture) injection of 1.5% lignocaine 30 ml (aqueous solution). Local anaesthetic solution may be seen in all three sections of the axilla. The artery and vein appear better defined and the separation of the vessels appears most marked in the mid-axilla after injection of local anaesthetic solution.

DISCUSSION

Traditionally, the methods used to study spread of local anaesthetic solutions have been based on radiography and cadaveric dissections. However, the ultrasound scan machine, available in many hospitals, may be an alternative technique. Correct positioning of the cannula may be visualized in relation to the axillary vessels. Radio-opaque dyes are unnecessary, as local anaesthetic solution may be "seen" with ultrasound. We found the distension of the "axillary sheath" was spindle shaped, and sections longitudinal to the axis of the axillary artery showed a curving of the axillary vessels around the head of the humerus.

The cross-sectional anatomy of the axilla was demonstrated clearly. In longitudinal section, the axillary vessels could be seen curving over the head of the humerus. The cannula and local anaesthetic solution were visualized better in real time scan, but photographs taken of "frozen" frames led to a loss in clarity of the boundaries. However, visible separation of the axillary vessels was caused by the local anaesthetic solution. The cords and nerves showed up as bright spots but were not visualized consistently in all patients. Perhaps the use of a probe frequency of 5 MHz may allow improved definition.

A limitation of this study was inability to quantify the volume of local anaesthetic on the ultrasound scan. The use of a computer interface with measurement of probe movements in the X, Y and X axes with graphic representation in three dimensions of sections taken close together might allow the volume of the distended tissues to be estimated and correlated with the volume of local anaesthetic injected.

ACKNOWLEDGEMENT

The Toshiba Ultrasound scan machine was on loan from Goldlite Pte. Ltd of Singapore.

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Br. J. Anaesth. (1989), **63**, 330–336

VASOPRESSIN RESPONSES DURING TRANSURETHRAL RESECTION OF THE PROSTATE

R. G. HAHN AND M. RUNDGREN

SUMMARY

The serum vasopressin (S-AVP) concentration, serum sodium concentration and osmolality, central venous pressure and fluid balance were measured during 10-min periods in 32 patients undergoing transurethral resection of the prostate. Concentration of S-AVP was unaffected by uncomplicated resection; irrigant absorption resulted in immediate increase in S-AVP concentration, but this increase could not explain the hypertension that occurred in some patients with absorption; a sudden decrease in the systolic arterial pressure was followed by a marked increase in S-AVP concentration; and extensive blood loss did not stimulate release of AVP, provided there was no associated arterial hypotension.

Transurethral resection of the prostate (TURP) may be accompanied by several changes in haemodynamic state and fluid balance [1,2]. Irrigating fluid may be absorbed into the circulation either directly or via the perivesical space to cause the "TURP syndrome" which is characterized by signs of water intoxication [3–5]. There is little information on the hormonal changes following various complications during TURP. In a patient who developed the TURP syndrome, the hormonal response to massive irrigant absorption was observed to counteract compensatory mechanisms [6]. At the end of an otherwise uneventful resection under extradural anaesthesia, the patient developed hypertension and complained of blurred vision. The serum concentration of sodium was found to be 115 mmol litre^{-1} and the serum concentration of arginine vasopressin (S-AVP) was 84.5 pg ml^{-1} (normal range 2.5–4 pg ml^{-1}) at an early stage of development of the syndrome. The absence of any obvious physiological stimulus for the AVP secretion in this situation [7] and the possibility that AVP may have been a causative factor in the hypertension [8] led us to study factors influencing S-AVP concentrations during TURP.

PATIENTS AND METHODS

Patients and surgical procedure

Following local Ethics Committee approval and informed patient consent, we studied 32 patients (mean age 71 yr, range 56–82 yr) undergoing TURP for benign prostatic enlargement. They were premedicated with oxazepam 25–50 mg orally. A central venous catheter (Drum-Cartridge) was inserted with the tip in the superior vena cava (confirmed by x-ray) and central venous pressure (CVP) was recorded continuously. Extradural analgesia was induced with 2 % mepivacaine 9–13 ml with adrenaline (Carbocain–adrenalin, Astra) to an upper sensory level of T4–T9. Ringer's solution (sodium content 130 mmol litre^{-1}) 10 ml kg^{-1} was administered i.v. during preparation of the patient for surgery in the lithotomy position. During TURP, the same solution was given at a rate of 50–150 ml/10 min i.v., depending on the estimated blood loss.

Volumetric fluid balance

During surgery the bladder was filled intermittently with 2.2 % glycine in water (Travenol, Bromma; osmolality 290 mosmol kg^{-1}). After operation, 0.9 % saline was used. The irrigating fluid bags were weighed before and after use. A sterile plastic drape was arranged to prevent spillover from the irrigating fluid returns. A

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Accepted for Publication: March 10, 1988.

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volumetric irrigating fluid balance was obtained at 10-min intervals throughout surgery (*collection period*) by closing the irrigating fluid inlet, emptying the bladder and replacing the irrigating fluid bag and the collecting bucket. Blood loss was calculated at the time of each volumetric fluid measurement, using the blood concentration of haemoglobin at the end of the collection period for reference [9]. The volume of irrigant absorbed was estimated as the difference between the volumetric fluid balance and the blood loss [10].

Analyses

Serial determinations of the serum osmolality and of the concentrations of blood haemoglobin (B-Hb), serum sodium (S-Na) and serum vasopressin (S-AVP) were made on venous blood samples obtained before and after extradural analgesia was induced, at the end of each collection period, and for 1 and 2 h after surgery. Serum osmolality was measured using a Roebling Micro-osmometer (Herman Roebling, Berlin) with a coefficient of variation of 0.5%. B-Hb was measured with a Coulter Counter S plus (Counter Electronics) and S-Na measured by flame photometry (AutoCal 543, Instrumentation Laboratory). Fifty duplicate samples from patients showed coefficients of variation of 1.2% for B-Hb and 0.6% for S-Na. The accuracy of the blood loss measurements was 100 ± 5% as checked by dispersion of known amounts of bank blood in irrigating fluid. Samples taken for measurement of S-AVP concentration were placed immediately on ice, centrifuged, and the serum stored at −70 °C until analysis by radioimmunoassay [11]. The sensitivity of the assay, as used in the present study, was 2.5 pg ml^{-1}. Samples with undetectable hormone were assumed to have this value for statistical calculations.

Patient groups

Based on the data obtained related to changes in fluid balance, each patient was classified to one of the following groups [10]:

Group I. No events ($n = 13$); blood loss < 800 ml and absorption of irrigant < 300 ml.

Group II. Extravascular absorption ($n = 5$); total irrigating fluid absorption > 300 ml and no significant decrease in S-Na (< 2 mmol litre^{-1}; $P > 0.05$) within 20 min of absorption.

Group III. Intravascular absorption ($n = 9$); irrigant absorption > 300 ml during the same collection period(s) as a decrease in S-Na > 2 mmol litre^{-1} ($P < 0.01$) was recorded.

Group IV. Increased blood loss ($n = 5$); blood loss > 800 ml and absorption of irrigant < 300 ml.

No patient received hypertonic saline solution or diuretics during the study. Erythrocyte concentrates were given after operation to the patients in group IV. Data were expressed as mean values (SD) when the data were distributed normally. When a skewed distribution occurred, median and range were used. Mann–Whitney's test, Wilcoxon's rank sum test and stepwise multiple regression were used for statistical analysis, as appropriate; the same tests were undertaken when performing statistical evaluation of the data on S-

TABLE I. *Data (mean (SD or range)) in 32 patients undergoing transurethral resection of the prostate*

	Group I ($n = 13$) (No events)	Group II ($n = 5$) (extravascular absorption)	Group III ($n = 9$) (intravascular absorption)	Group IV ($n = 5$) (increased blood loss)
Patient age (yr)	72 (5)	67 (9)	68 (8)	72 (7)
Serum creatinine concn before TURP (μmol litre^{-1})	130 (52)	121 (43)	102 (33)	96 (10)
Resection time (min)	41 (10)	44 (11)	48 (8)	68 (20)
Weight of resectate (g)	17 (7)	24 (18)	27 (8)	40 (20)
Blood loss (ml)	192 (66–513)	478 (247–1143)	708 (280–934)	1260 (812–1530)
Irrigating fluid absorption (ml)	59 (0–281)	636 (310–1683)	994 (616–2811)	201 (143–280)
Maximum change in serum sodium concn (mmol litre^{-1})	−0.8 (1.6)	−1.6 (0.8)	−9.3 (3.5)	0.0 (3.1)
Maximum change in CVP (mm Hg)	+1 (−1 to +4)	0 (−2 to +1)	+4 (0 to +7)	−2 (−3 to 0)

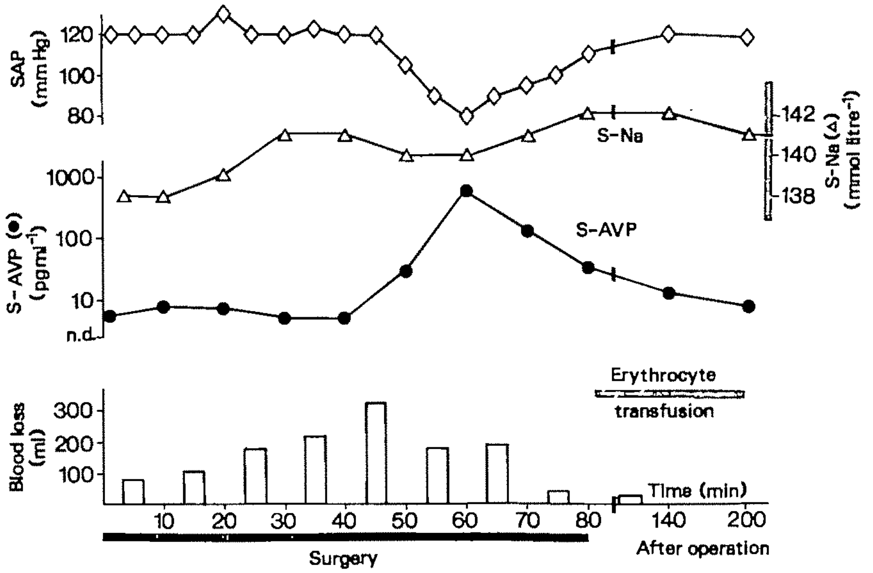

FIG. 1. Systolic arterial pressure, serum AVP and sodium concentrations, and blood loss (bars) in one patient undergoing TURP. Total blood loss was 1260 ml, while the irrigant absorption was only 201 ml. Note log scale for S-AVP concentration. n.d. = Not detectable.

AVP concentrations set to the lower limit of detection in the assay used.

RESULTS

Details of the patients studied are shown in table I.

Changes in S-AVP during TURP

Sudden episodes of hypotension to 80 mm Hg or less were associated with marked increases in S-AVP concentrations (figs 1, 2). Two patients in group I had increased S-AVP concentrations (70.0 and 79.1 pg ml^{-1}, respectively) when the arterial pressure decreased to 75 mm Hg. One of these incidents was interpreted as a vasovagal syndrome (bradycardia and no preceding change in CVP), whereas the second occurred in association with increased administration of fluid (CVP increased by 3 mm Hg). One patient in group III had a reaction interpreted as a vagal reflex accompanied by increased S-AVP concentration (maximum 283.3 pg ml^{-1}) before absorption of irrigating fluid was noted (fig. 2). Three patients in group IV had S-AVP concentrations increased to 348.4, 591.1 (fig. 1) and 20.6 pg ml^{-1}, respectively, in association with sudden hypotension; hypovolaemia obviously contributed to the hypotension, as it was preceded by increased blood loss and changes in the CVP (−3, −3 and −2 mm Hg, respectively).

In patients without hypotension, observations in the different groups were as follows:

Group I (11/13). Only small, non-significant changes in S-AVP concentration were observed. The median S-AVP concentration after induction of anaesthesia was 2.7 pg ml^{-1} (range 2.5–4.1 pg ml^{-1}) and during TURP 2.6 pg ml^{-1} (range 2.5–5.7 pg ml^{-1}) (Wilcoxon's test, ns). Changes in the serum osmolality during each TURP were smaller than, or close to, the limit of analysis.

Group II (5/5). Extravascular absorption of irrigating fluid was accompanied by increased S-AVP concentrations. The maximum S-AVP concentrations during absorption were 5.0, 11.8, 13.8, 19.1 and 38.9 pg ml^{-1}, respectively. However, one of these patients had an increased S-AVP concentration after induction of extradural analgesia (29.1 pg ml^{-1}), while another patient exhibited a slow decrease in the systolic arterial pressure to 85 mm Hg at the time of absorption. In all other patients, changes in systolic arterial pressure were within ± 5 mm Hg.

Group III (8/9). The S-AVP concentration was greater during collection periods with intravascular absorption (median 6.1 pg ml^{-1}; range

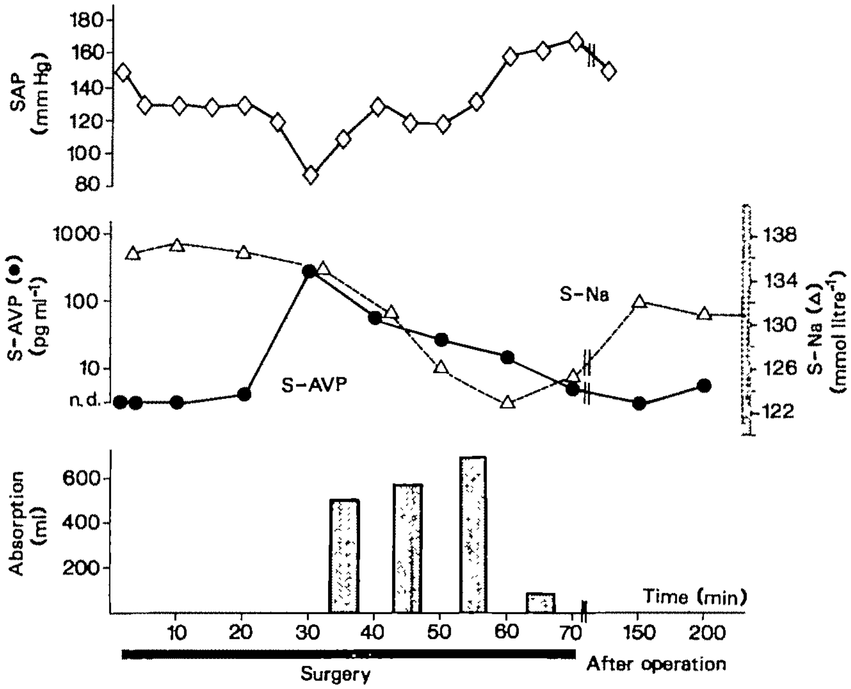

FIG. 2. Systolic arterial pressure, serum AVP and sodium concentrations, and volume of irrigant absorbed (bars) in one patient with sudden hypotension, interpreted as a vasovagal reaction, after 30 min of TURP surgery. Later, there was irrigant absorption amounting to 1900 ml. Note the late absorption hypertension. n.d. = Not detectable.

2.5–6.9 pg ml^{-1}) compared with periods when there was no absorption (median 2.8 pg ml^{-1}; range 2.5–4.5 pg ml^{-1}) (Wilcoxon's test, $P < 0.01$). There was an increase in S-AVP during absorption in all but one patient. Changes in serum osmolality during TURP exceeded the precision of serial determinations in four patients, in whom osmolality decreased by 2–3%.

Group IV (2/5). Two patients in this group had a stable arterial pressure in spite of a large blood loss (1260 and 1425 ml) and they had normal S-AVP concentrations (2.9 (0.6) pg ml^{-1}) during the surgical procedure. Also, CVP was largely unaffected (±1 mm Hg) by blood loss in these patients.

S-AVP and absorption hypertension

In group III, systolic arterial pressure increased in four of the nine patients by 25 mm Hg or more after 15–25 min of absorption. In contrast, the S-AVP response to absorption was immediate. Furthermore, one patient had a large absorption (1900 ml) following a vasovagal reaction, but did not develop hypertension earlier than the other patients with absorption hypertension, in spite of a substantial increase in the S-AVP concentration (fig. 2). With the exception of the patient presented in figure 2, AVP seemed not to cause hypertension in any patient in group III, as the S-AVP concentrations during absorption in patients with hypertension (6.4, 4.9 and 6.1 pg ml^{-1}) were similar to those in patients without hypertension (6.1, 6.1, 2.5, 5.1 and 6.9 pg ml^{-1}).

Variables related to S-AVP changes during absorption

Although increased S-AVP concentrations were observed during intravascular absorption (group III), no significant correlation was found between this variable and the amount of absorbed irrigating fluid. Furthermore, no correlation was found between S-AVP concentration and the CVP, blood loss, arterial pressure, serum osmolality or changes in the serum sodium concentration for all collection periods during irrigant absorption (stepwise multiple regression). However, collection periods with both irrigating fluid absorption and increased CVP were always associated with increased S-AVP concentration ($n = 8$), whereas unchanged or decreased CVP was accompanied usually by reduced concentrations of AVP. As expected, fluid retention (fluid absorption minus blood loss) was larger during collection periods with increased S-AVP concentrations (median 284 ml, range 50–616 ml; $n = 10$) than during collection periods with decreased values (median −10 ml, range −128 to 372 ml; $n = 7$) (Mann–Whitney test, $P < 0.05$).

S-AVP and i.v. fluid overload

An increase in CVP of 2–4 mm Hg was not associated with irrigant absorption in two patients during TURP and in four patients during follow-up. These events were interpreted as i.v. fluid overload [2] and were not associated with increased S-AVP concentrations.

Postoperative changes in S-AVP

Sudden increases in S-AVP concentrations after operation were common in patients with intravascular irrigant absorption (group III). These increases correlated with nausea or unstable arterial pressure, or both; the median S-AVP concentration in group III patients at 1 or 2 h after completion of resection was 7.9 pg ml^{-1} (range 2.5–24.3 pg ml^{-1}). In the other groups only occasional postoperative increases in AVP concentration were found.

DISCUSSION

The aim of the present study was to investigate the effects of complications during TURP on release of AVP and therefore we avoided those conditions known to affect secretion of AVP. The potential stimulant effect of morphine [12] was avoided by the use of oxazepam as premedication. Changes in serum osmolality by fluid absorption were minimized by use of an isotonic irrigating fluid. Extradural analgesia was used because it has been reported to reduce the effect of surgery on release of AVP [13].

We have demonstrated that uncomplicated TURP surgery under extradural anaesthesia did not stimulate secretion of AVP. However, several changes did cause release of AVP. Sudden hypotension was found to be the most potent stimulus for release of AVP. On the other hand, excessive blood loss, accompanied by a decrease in CVP, did not stimulate AVP secretion, provided that normotension was maintained. This is in agreement with observations in animals [14]. Recent studies in man also support the concept that high-pressure rather than low-pressure baroreceptors are important in control of AVP secretion [15].

It is concluded that *extravascular absorption of irrigating fluid* stimulated release of AVP, although in two of the patients in group II other causes may have been responsible for the changes observed. Postoperative decrease in urinary excretion has been reported in association with extravascular fluid absorption [16, 17]. The direct measurement of AVP in our study suggests that this water retention may be mediated via antidiuretic hormone. The mechanism of release of AVP is obscure, but it is possible that a stimulatory effect similar to that of visceral traction [18] may have contributed.

Intravascular absorption of irrigating fluid was followed immediately by increase in secretion of S-AVP (fig. 3). Doubling of S-AVP concentration results in water retention [7], which may aggravate the dilution hyponatraemia caused by absorption of irrigant (table I). As the hypervolaemia and hypo-osmolality induced by fluid absorption should inhibit release of AVP, it is possible that increased serum concentrations of glycine may, directly or indirectly, stimulate secretion of AVP. There is no experimental evidence for this hypothesis; on the contrary, application of strychnine, an antagonist of glycine, to the ventral surface of the brainstem in animals has been shown to induce release of AVP [19].

CVP is thought to be an excellent guide for assessing absorption of irrigating fluid [2, 20]. This was confirmed by our observations in most patients of this study (table I). However, this may be masked by concomitant blood loss [21], and as increases in CVP may occur without simultaneous absorption, it is sometimes unreliable.

Absorption of irrigating fluid may be associated with hypertension [1, 4]. The patient described in the introduction, who developed hypertension in association with irrigating fluid absorption, had an increased concentration of S-AVP (84.5 pg ml^{-1}) which may have contributed to the hypertension. However, it is unlikely that AVP was a main factor in the development of hypertension occurring in association with irrigating fluid absorption in the present study. There were only minor differences in S-AVP concentration during absorption between patients with and without hypertension (although the numbers are small).

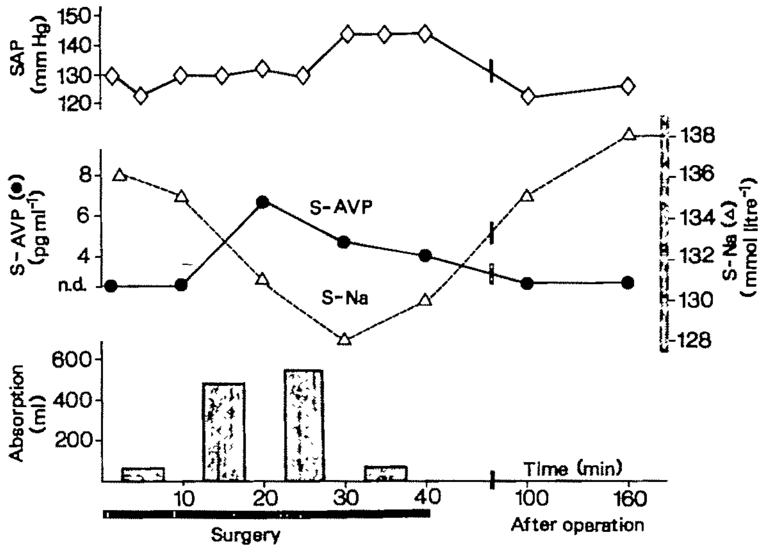

FIG. 3. Systolic arterial pressure, serum AVP and sodium concentrations and volume of irrigant absorbed (bars) in one patient with a total operative blood loss of 720 ml and irrigant absorption amounting to 1126 ml. Note the absorption hypertension. n.d. = Not detectable.

The S-AVP concentrations achieved during absorption were smaller than those considered generally to affect arterial pressure in subjects with intact baroreflexes [22]. Furthermore, the increase in S-AVP concentration and hypertension were not time-related.

Postoperative increases in S-AVP concentration were common in patients with absorption of intravascular fluid during TURP surgery (group III). In contrast to that seen during the surgical procedure, these events correlated with factors known to stimulate secretion of AVP, such as nausea and unstable arterial pressure [7,23]. Nausea may occur after absorption of large amounts of irrigating fluid, possibly because of glycine toxicity [24].

ACKNOWLEDGEMENT

This study was supported by grants from the Medical Faculty at the Karolinska Institute and the Swedish Medical Research Council (project No. 06553).

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VASOPRESSIN AND AMINO ACID CONCENTRATIONS IN SERUM FOLLOWING ABSORPTION OF IRRIGATING FLUID CONTAINING GLYCINE AND ETHANOL

R. G. HAHN AND M. RUNDGREN

SUMMARY

Absorption of glycine solution during transurethral resection of the prostate (TURP) changes the serum concentrations of most non-essential amino acids and inhibits diuresis by stimulating release of vasopressin. Ethanol was used as a marker to detect the absorption of irrigant. Measurements of the serum concentrations of vasopressin and amino acids were made in eight patients with absorption volumes from 427 to 1906 ml. Ethanol did not alleviate the vasopressin response to glycine absorption, but changes in the amino acid concentrations in serum became less pronounced than when glycine alone was used.

It is well known that, during transurethral resection of the prostate (TURP), irrigating fluid may be absorbed into the circulation directly or through the perivesical space. Recently, a new method of detecting this complication before symptoms develop has been described. Ethanol is added to the irrigating fluid so that absorption can be monitored by measuring ethanol in expired air [1, 2]. Earlier studies have shown that absorption of irrigant containing glycine alone stimulates release of arginine vasopressin (AVP) [3] and causes marked changes in amino acid pattern in serum [4]. We therefore investigated the serum concentrations of AVP and amino acids when irrigating fluid containing both glycine and ethanol was absorbed.

METHODS AND RESULTS

We studied 50 patients undergoing TURP for benign prostatic enlargement. Appropriate Ethics Committee and patient consent were obtained. Oxazepam 25–50 mg was given by mouth as a premedicant. Extradural anaesthesia was induced with 2% mepivacaine plus adrenaline. To prevent hypotension during the onset of extradural anaesthesia, Ringer's acetate 10–12 ml kg^{-1} or dextran 40 100–150 ml was given i.v. and during surgery these i.v. fluids were given at a rate to compensate for the visually estimated blood loss. An intermittent filling technique of the bladder was used. The irrigating fluid used during resection was water containing 1.5% glycine and 2% ethanol (w/v) (osmolality 650 mosmol kg^{-1}) (Travenol, Sweden). After operation, 0.9% saline was used. Every 5 min during surgery the end-expiratory ethanol concentration was measured with an Alcolmeter S-D2 (Lions Ltd, Barry, Wales). The volumetric fluid balance was obtained during 10-min periods of TURP by changing the irrigating fluid bag and the (heparinized) collection bucket, and subsequent careful measurement of all fluid volumes. Each volumetric fluid balance was corrected for blood loss to give the degree of absorption. Measurements of the serum sodium and blood haemoglobin concentrations and of osmolality were made before and after extradural anaesthesia was induced, during 10-min periods during TURP, and for 30 min or 1 h (or both) after operation [1–5]. Additional blood samples from each 10-min period were immediately placed on ice, centrifuged, and the serum stored at −70 °C for later analysis.

The courses of the 50 operations were analysed, and in eight patients the data indicated that

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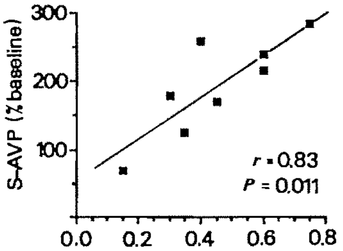

FIG. 1. Change in the serum vasopressin concentration (S-AVP) during transurethral prostatic resection, expressed as the quotient between the highest value recorded during surgery by the value obtained just before surgery commenced *v.* the degree of irrigating fluid absorption, as indicated by the highest ethanol concentration recorded in expired breath (EB-ethanol) during operation.

absorption had occurred only by the i.v. route; there was a significant decrease in serum sodium concentration (2 mmol litre^{-1} or more) and an increase in the end-expiratory concentration of ethanol during the same 10-min periods as absorption was measured volumetrically [1–5]. These eight operations (patient mean age 73 yr, range 66–83 yr) were selected for further analysis.

The concentrations of amino acids in the serum samples from the selected patients were measured with a Liquimat III (Kontron, Zürich, Switzerland; coefficient of variation < 10%) and AVP with a radioimmunoassay method [3]. The sensitivity of the AVP assay, as used in the present study, was 2.0 pg ml^{-1}. Serum samples with undetectable concentrations of the hormone (four of 43) were set to this value in statistical calculations. Results are presented as the mean value and the standard deviation (SD) or the range. The methods of statistical analysis were simple linear regression and the paired t test.

The mean volume of irrigant absorbed as measured volumetrically during the eight selected operations was 980 ml (range 425–1906 ml). The mean change in serum concentration of sodium was -6 mmol litre^{-1} (-2 to -8 mmol litre^{-1}), and the blood haemoglobin -2.2 g dl^{-1} (-3.5 to -1.3 g dl^{-1}). The mean blood loss was 650 ml (150–1256 ml) and the weight of the resected prostatic tissue 25 g (11–50 g).

AVP and osmolality. During irrigant absorption the S-AVP concentration increased in seven of eight patients and was related linearly to the end-expiratory concentration of ethanol (fig. 1). The S-AVP concentration during irrigating fluid absorption (subject mean (SD) 7.4 (3.8) pg ml^{-1}) was significantly greater than at the start of surgery (3.2 (1.4) pg ml^{-1}) and after resection (3.9 (1.6) pg ml^{-1}) ($P < 0.04$). There was an increase in the serum osmolality of 5 (3) mosmol kg^{-1}, which was most pronounced (10 mosmol kg^{-1}) during the resection with the greatest absorption.

The serum concentration of glycine varied between 296 and 12080 µmol litre^{-1}. A median fraction of 8% of the glycine absorbed during a 10-min period of surgery could be detected in serum at the end of the same period; the greatest values (up to 33%) were obtained during massive absorption (> 500 ml/10 min). There was a significant linear correlation between the increase in serum glycine during any 10-min period where irrigant absorption was recorded volumetrically, and the volume of irrigant absorbed during that period ($r = 0.58$; $P < 0.005$; $n = 25$) and the change in serum concentration of sodium ($r = -0.72$; $P < 0.001$). Postoperative elimination curves indicated a half-life ($T_{\frac{1}{2}}$) of approximately 60 min for glycine.

All preoperative serum concentrations of amino acids were within the normal range. For each amino acid the total change in concentration from just before induction of extradural anaesthesia to the end of TURP was less than 20% except for: alanine +30% ($P < 0.05$), asparagine +50% ($P < 0.05$), glycine +2000% ($P < 0.001$), serine 60% ($P < 0.02$), tyrosine -40% ($P < 0.001$), and threonine +40% ($P < 0.01$). Before operations the aggregate serum concentration of non-essential amino acids other than glycine and serine was 1757 (745) µmol litre^{-1} (mean (SD)), and at the end of the resections it was 1588 (756) µmol litre^{-1} (paried t test; ns). The aggregate sum of essential amino acids did not show any significant changes.

COMMENT

TURP is often uncomplicated and a larger patient group was studied to identify eight patients in whom irrigant had been absorbed by the intravascular route. In a previous study we found that, in contrast to uncomplicated TURP performed during extradural anaesthesia, i.v. absorption of isotonic (2.2%) glycine solution was associated with increased AVP concentrations in serum, usually to approximately twice the value found at times of no absorption in the same patient [3]. This may aggravate the water retention that may follow absorption of irrigant, and thus increase the risk of water intoxication. Although it has been shown that the serum concentrations of ethanol obtained in the present study inhibit baseline vasopressin secretion in healthy elderly volunteers [6], our results show that they do not alleviate the AVP response to glycine absorption.

The changes in amino acid concentrations in serum following absorption of irrigating fluid containing glycine and ethanol exhibit the same general features as those we described recently for isotonic glycine [4]. However, the present study suggests that absorption of a solution containing both glycine and ethanol is followed by lesser changes in the serum amino acid pattern than when a solution containing glycine alone is absorbed. The mean absorption of approximately 1 litre of 1.5% glycine+2% ethanol resulted in increases in serine, alanine and threonine approximately 30% as great as those recorded previously for 1 litre of isotonic glycine [4]. Furthermore, the aggregate sum of non-essential amino acids other than glycine and serine did not change. In contrast, the aggregate sum increased in direct proportion to the amount of glycine absorbed when an isotonic solution of glycine was used, an increase that coinicided with the onset of symptoms of glycine toxicity [4].

ACKNOWLEDGEMENTS

We thank Roland Eklöf for performing the amino acid analyses. The study was supported by grants from the Medical Faculty at the Karolinska Institute and the Swedish Medical Research Council (project No. 06553).

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Br. J. Anaesth. (1989), **63**, 340–342

PROPHYLACTIC EPHEDRINE DURING SPINAL ANAESTHESIA: DOUBLE-BLIND STUDY IN PATIENTS IN ASA GROUPS I–III

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The use of ephedrine in addition to the routine infusion of i.v. fluids to control hypotension during spinal block is well established [1]. It has been shown that premedication with ephedrine prevents the occurrence of severe changes in the central circulation in elderly patients during high extradural block [2].

The use of prophylactic vasopressor therapy has not been established for specific patient categories. The aim of this study was to evaluate the clinical use of prophylactic ephedrine before spinal anaesthesia, in patients assigned to different ASA classifications.

METHODS AND RESULTS

The project was approved by the Danish health authorities and by the Ethics Committee of Western Zealand; verbal informed consent was obtained from all subjects.

We studied 48 patients scheduled to undergo surgical procedures on the lower extremities or lower abdomen under spinal anaesthesia. At the preoperative visit, all patients were assessed clinically and, according to their medical condition, they were assigned to one of the American Society of Anesthesiologists (ASA) Physical Status Classes I–V [3]. We studied 16 patients in each of ASA groups, I, II and III; patients assigned to ASA IV and V classes were not included, for ethical reasons.

Patients in each ASA group were allocated by a double-blind random process to receive either ephedrine 12.5 mg i.v. and 37.5 mg i.m., or saline placebo. Premedication comprised diazepam 5–15 mg orally 60 min before the scheduled start of procedure. Immediately before anaesthesia, 7 ml/kg body weight of an isotonic sodium–glucose solution was administered i.v. over 20 min. Spinal anaesthesia was performed with a 25- or 26-gauge spinal needle with patients in a sitting or lying position. Bupivacaine 3 ml without adrenaline (Marcain isobar 5 mg ml^{-1}) was injected into the subarachnoid space over 15 s at L2–3 or L3–4. Simultaneously, ephedrine 12.5 mg or placebo was administered i.v. according to the randomization. Ephedrine 37.5 mg or placebo was injected i.m. Patients were placed in a horizontal position and arterial pressure and heart rate were measured after 1 min and every 5 min for 40 min. The lowest mean arterial pressure was noted. The level of analgesia was tested by pinprick 20 min after the subarachnoid injection.

SUMMARY

Forty-eight patients scheduled to undergo spinal anaesthesia were allocated to three groups of 16 each according to ASA classification I–II–III. Each patient received a fluid load of 7 ml kg^{-1} and either ephedrine 12.5 mg i.v. and 37.5 mg i.m., or placebo. Twelve patients in the placebo groups developed a maximal decrease in mean arterial pressure exceeding 20%. Five of these (one in ASA II and four in ASA III) developed a decrease exceeding 33% and required treatment. In ASA risk group III, all patients in the placebo group had a decrease in mean arterial pressure exceeding 20%; in 50% of these patients, the decrease exceeded 33%. We conclude that prophylactic ephedrine is desirable for spinal anaesthesia, especially in ASA III patients.

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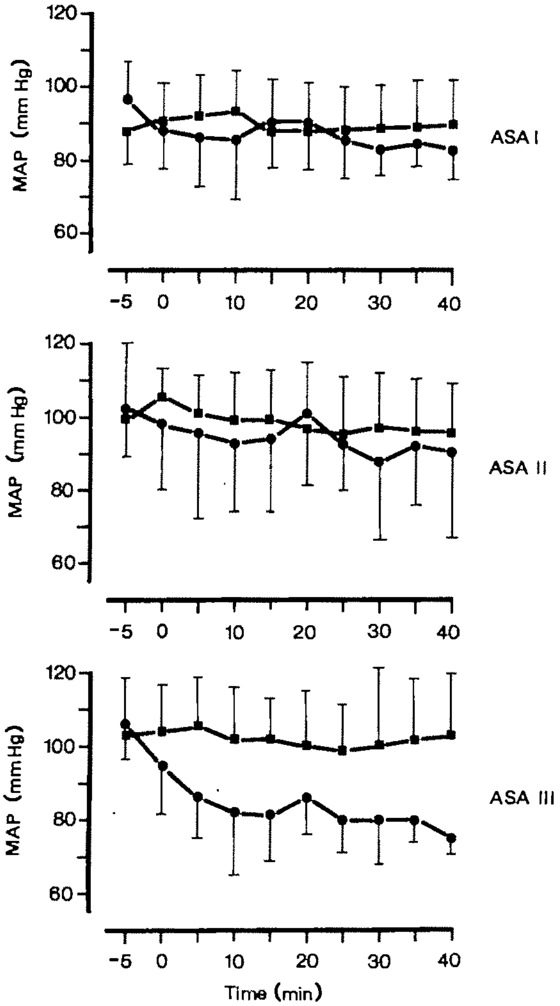

FIG. 1. Mean (SD) arterial pressure in ASA risk groups I, II and III after ephedrine (■) or placebo (●).

During anaesthesia isotonic sodium–glucose solution 7 ml kg^{-1} was given i.v. during the first 20 min (0.35 ml kg^{-1} min^{-1}). If the reduction in mean arterial pressure exceeded 20%, the rate of infusion was increased. If the reduction in mean arterial pressure exceeded 33% or if systolic pressure decreased to less than 80 mm Hg, patients were treated according to our usual clinical practice by head-down tilt, increased fluid infusion, oxygen, ephedrine and infusion of albumin or blood. If sedation was required, midazolam was administered i.v.

Arterial pressure was measured using a mercury manometer with a cuff on the upper arm. Mean arterial pressure (MAP) was calculated as:

$$\text{diastolic pressure} + \frac{\text{systolic} - \text{diastolic}}{3}$$

The maximum change in mean arterial pressure (dMAPmax) was calculated as the difference between preanaesthetic pressure (preMAP) and lowest pressure in the 40-min observation period during anaesthesia (anMAP). ECG was monitored.

Wilcoxon rank sum test was used for comparison of paired data within groups, and Mann–Whitney rank sum test for unpaired data between groups. Correlation analysis was performed by Spearman's rank difference method. $P < 0.05$ was considered significant.

Within each ASA group, the patients given ephedrine and placebo were comparable with respect to age, height, level of anaesthesia, cardiac risk index, and pre-anaesthetic arterial pressure.

In ASA I group, MAP in the placebo-treated patients decreased by 14.0 (SD 9.5) mm Hg, but it increased in the ephedrine-treated group (1.8 (6.2) mm Hg) ($P < 0.05$). In the ASA II group, MAP in ephedrine- and placebo-treated patients was not significantly different. In the ASA III group there was a marked reduction in MAP in the placebo-treated patients (30.8 (12.2) mm Hg) that differed significantly from that in the ephedrine-treated group (5.2 (7.2) mm Hg) ($P < 0.01$). All placebo-treated patients in ASA III group had a reduction in MAP exceeding 20%: in 50% of these, the decrease exceeded 33%.

In total, 12 patients who received placebo had maximum hypotension exceeding 20% and were treated with increased i.v. infusions of electrolyte solution. Five of these (one in ASA II and four in ASA III) had a decrease in MAP exceeding 33% and were treated according to our clinical practice. No patient developed systolic pressures less than 75 mm Hg during anaesthesia.

In four of the 12 patients, the maximum decrease in MAP occurred within the first 5 min after the subarachnoid injection of bupivacaine, while in three other patients it developed more than 30 min after injection.

No significant correlation was found between change in MAP and age, cardiac risk index, height or level of anaesthesia. Changes in heart rate did not differ between groups. Hypertension or tachycardia was not observed following administration of ephedrine. No patient developed angina, cardiac arrhythmia or signs of cardiac decompensation during or in the first hours after anaesthesia. No patient had postdural puncture headache or neurological sequelae.

For sedation 12 patients were given midazolam 1.25–5 mg i.v. during the first 40 min of anaesthesia. The midazolam-treated patients were distributed equally between all groups and their cardiovascular changes did not differ from those of the patients not given midazolam.

Two patients (both in the placebo group) had a peroperative blood loss exceeding 500 ml. In one, bleeding was associated with hypotension of 30 %, and the patient was treated by infusion of blood and Ringer's lactate solution. No significant difference was seen in peroperative blood loss between groups.

COMMENT

Spinal block is likely to be accompanied by hypotension caused by reduction in stroke volume and cardiac output and a reduction in systemic vascular resistance [4]. Several authors recommend that a decrease in mean arterial pressure of more than 30 % less than the preanaesthetic value or a systolic pressure less than 75 mm Hg are indications for corrective measures [5, 6]. As the reduction in preload is the main cause of hypotension during spinal block, the prophylactic infusion of approximately 500 ml of isotonic fluid is common clinical practice.

Ephedrine is a sympathomimetic amine which stimulates alpha- and beta-receptors and release of catecholamine stores from terminal nerve endings. Its positive inotropic and chronotropic actions increase cardiac output, venous return and arterial pressure. It may cause tachycardia and arterial hypertension and, by stimulating the central nervous system, produce vertigo, headache or vomiting. No such untoward effects were seen in this study.

Our data show that, in 48 patients distributed evenly to ASA risk groups I, II and III, prophylactic administration of ephedrine prevented hypotension; the only preanaesthetic variable affecting this was the ASA classification of the patient. Variables such as age and cardiovascular risk group were not significant. Other variables which may affect cardiovascular changes during spinal block include low haemoglobin concentration, low albumin concentration, disturbances of electrolyte balance, acid–base status and arterial hypertension. However, our database was too small to permit examination of these factors.

We conclude that it is appropriate to administer ephedrine i.v. and i.m. routinely at induction of spinal anaesthesia, especially in patients of ASA class III, although the combination of fluid load and a vasoconstrictor should be used cautiously in poor risk patients.

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Br. J. Anaesth. (1989), **63**, 343–345

SEDATION DURING SPINAL ANAESTHESIA: A CASE FOR THE ROUTINE ADMINISTRATION OF OXYGEN

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SUMMARY

We have studied the effect of sedation with midazolam on arterial oxygen saturation during spinal anaesthesia in two groups of patients: one group received supplementary oxygen, the other group breathed room air. A significant reduction in oxygen saturation was observed in patients not receiving supplementary oxygen; six of 15 patients in this group developed hypoxaemia or severe hypoxaemia which was corrected immediately by administration of oxygen. There were no episodes of hypoxaemia in any patient in the group receiving supplementary oxygen. It is concluded that oxygen should be administered routinely to patients receiving sedatives during spinal anaesthesia.

Patients undergoing surgery with regional anaesthesia are frequently sedated, as many prefer to have no recall of their stay in the operating theatre. Midazolam is used commonly for this purpose and may be preferable to diazepam, as it is associated with a greater degree of amnesia [1]. The administration of additional oxygen to these patients is practised by most anaesthetists, but reference works on local anaesthesia make only cursory mention of the use of oxygen. A reduction in arterial oxygen saturation has been reported in three patients undergoing surgical procedures with regional anaesthesia and sedated with midazolam [2]. The aim of this study was to investigate the effects of the combination of spinal anaesthesia and sedation with midazolam on oxygen saturation.

METHODS AND RESULTS

Thirty patients undergoing transurethral resection of the prostate (TURP) gave informed consent to participate in the study, which was approved by the Hospital Ethics Committee. FVC and FEV_1 were measured in all patients, using a Vitalograph. No premedication was prescribed. On the patient's arrival in the anaesthetic room, baseline heart rate, arterial pressure (AP) and arterial oxygen saturation (Sa_{O_2}) in the ear lobe [3] were recorded using a continuous ECG display, an automatic arterial pressure recorder (Dinamap) and a pulse oximeter (Ohmeda Biox 3700), respectively. The rate of ventilation was counted over a 1-min period. Patients were given Hartmann's solution 500 ml i.v. and spinal anaesthesia was induced with 0.5% bupivacaine 3 ml in 8% glucose injected over 30 s at the L2–3 or L3–4 space with patients in the lateral position. The upper level of the block was assessed by loss of sensation to pinprick and the patient placed in the lithotomy position. The measurements were then repeated.

Patients were allocated randomly to one of two groups: group A received oxygen 4 litre min^{-1} from a Hudson mask; group B breathed room air. Incremental 1-mg i.v. doses of midazolam were administered at 3-min intervals until Verrill's sign [4] was achieved. Further increments were given as required during the procedure to maintain this level of sedation. A clear, unobstructed airway was maintained at all times. Heart rate, ventilatory rate, AP and Sa_{O_2} were recorded at 3-min intervals from the institution of the intrathecal block until the end of the procedure. Sa_{O_2} was recorded only when the plethysmographic waveform on the oximeter was normal. Supplementary oxygen was administered to patients in group B if Sa_{O_2} was

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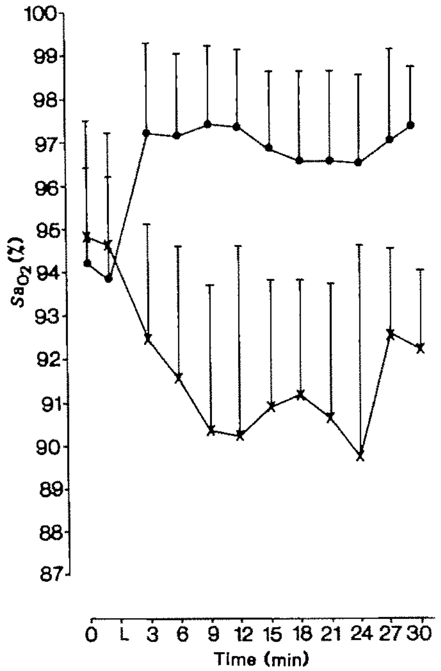

FIG. 1. Mean (SD) Sa_{O_2} values in group A (●) and group B (x) at various times after the administration of midazolam. 0 = Baseline Sa_{O_2}; L = Sa_{O_2} after assumption of the lithotomy position.

sustained between 85 and 89% ("hypoxaemia") for 5 min or decreased to less than 85% ("severe hypoxaemia") at any time.

Student's unpaired *t* test was used to compare the demographic data and the Sa_{O_2} values.

The mean (SD) values of the following variables did not differ significantly between groups A and B (respectively): age 77.8 (7.9) *v.* 74.1 (9.4) yr; weight 73 (13.2) *v.* 70.3 (8.9) kg; height 173 (6.5) *v.* 170.9 (7.6) cm; spirometry (FEV_1) 1.85 (0.92) *v.* 1.99 (0.43) litre, total dose of midazolam 3.93 (1.2) *v.* 4 (1.8) mg; weight of prostatic tissue resected 24.7 (31.8) *v.* 29.4 (29.1) g. The median height of anaesthesia to pinprick was T8 (range T6–T11) in both groups.

The baseline rate of ventilation was similar in both groups (14.9 (2.9) *v.* 13.1 (1.7) b.p.m.), but increased significantly ($P < 0.01$) after the administration of midazolam to a maximum of 21.2 (4.1) and 22.7 (5.1) b.p.m. in groups A and B, respectively. Baseline Sa_{O_2} was comparable in both groups (94.2 (3.3) *v.* 94.8 (1.7)%) and was not reduced significantly following assumption of the lithotomy position. Sa_{O_2} in patients in group A was significantly higher than that in group B throughout the procedure ($P < 0.001$) following the administration of midazolam (fig. 1). The reduction in Sa_{O_2} from baseline in group B was significant also at each time of measurement ($P < 0.005$ at 3, 27 and 30 min; $P < 0.001$ at all other times).

Hypoxaemia developed in four patients, and severe hypoxaemia in two patients in group B. The reduction in Sa_{O_2} was not associated with hypotension, airway obstruction or apnoea, but was associated closely with the administration of midazolam and the achievement of the desired level of sedation. The administration of oxygen corrected the hypoxaemia in all patients. One patient with hypoxaemia developed a junctional rhythm and broadened QRS complexes. Sinus rhythm was restored with the administration of oxygen.

COMMENT

A significant reduction in Sa_{O_2} may occur when spinal anaesthesia is combined with sedation induced by midazolam. Similar desaturation has been reported during upper gastrointestinal endoscopy when midazolam was used for sedation, and was prevented by the routine administration of oxygen [5]. Although moderate transient reductions in Sa_{O_2} may be considered acceptable in young, healthy patients, they should be avoided in the elderly patient with ischaemic heart disease. This was illustrated by the association of arrhythmia with hypoxaemia in one of the patients withdrawn from group B.

No constitutional factor was significantly different in those patients developing hypoxaemia, but the number of patients studied was small. Midazolam is known to cause central respiratory depression resulting in a reduction in total lung capacity, maximal breathing capacity and tidal volume, whilst the rate of ventilation is increased; significant reductions in Sa_{O_2} have followed the administration of midazolam 0.2 mg kg^{-1} to young healthy volunteers [6]. The elderly patients in this study received smaller doses but demonstrated similar findings, possibly because of the combination of a degree of deafferentation and sedation. The physiological effects of age on pulmonary function place elderly patients at greater risk of developing hypoxaemia. Increased closing volume encroaches on tidal ventilation, resulting in increased intrapulmonary shunting and an increased alveolar to arterial difference in oxygen tension. The assumption of the lithotomy position, with its attendant reduction in functional residual capacity, further aggravates ventilatory function.

We conclude that spinal anaesthesia combined with sedation should not be used without the administration of additional oxygen, unless a pulse oximeter is available to monitor Sa_{O_2}.

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Br. J. Anaesth. (1989), 63, 346–347

HYPOXAEMIA AFTER INHALATION OF 50% NITROUS OXIDE AND OXYGEN

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SUMMARY

We have investigated, in volunteers, the effect of inhaling 50% nitrous oxide in oxygen on subsequent oxygenation. Subjects breathed either 50% nitrous oxide in oxygen or 50% nitrogen in oxygen during hyperventilation and normal ventilation. Arterial oxygen saturation and end-expired oxygen concentrations were lower after 50% nitrous oxide in oxygen than after the other mixture with both patterns of ventilation and were lowest after hyperventilation with 50% nitrous oxide in oxygen.

It is well known that hypoxaemia may occur when an inspired gas mixture containing 70–80% nitrous oxide is changed to air [1]. It is commonly thought that this does not occur after 50% nitrous oxide in oxygen. Unpublished observations from our department suggested that women given Entonox (50% nitrous oxide in oxygen) for pain relief during labour became hypoxaemic between uterine contractions. Hyperventilation during contractions is common and itself may promote hypoxaemia [2] because of reduced ventilatory drive caused by hypocapnia. This study was performed to determine if inhalation of Entonox may be followed by hypoxaemia in normal (non-pregnant) subjects and to assess the additional effect of hyperventilation.

METHODS AND RESULTS

The study was approved by the District Ethics Committee and 10 subjects (eight male) of mean age 28 yr (range 26–34 yr) gave informed consent to be studied. Each subject inhaled gas mixtures composed of 50% nitrous oxide in oxygen, 50% nitrogen in oxygen and 79% nitrogen in oxygen. The mixtures were made up from their constituent gases into Douglas bags with an accuracy of 1%, confirmed by mass spectrometry (Centonic Medical MGA 2000). The mixtures were inhaled via a low resistance breathing system incorporating a tightly applied non-rebreathing mask. The mass spectrometer sampled from the mask for measurement of end-expired oxygen concentrations (FE'_{O_2}) and a pulse oximeter (Nellcor N-100) was applied to the subject's first finger to measure changes in oxygen saturation (Sa_{O_2}). The outputs from these instruments were displayed on a chart recorder.

Baseline values of FE'_{O_2} and Sa_{O_2} were taken as the lowest values obtained during an initial 10-min period, during which the subject breathed room air. Each gas mixture was inhaled for 2 min of hyperventilation and 10 min of resting ventilation. There was a 15-min measurement period (during which the subject breathed room air) and a 5-min rest period after each administration. The sequence was random.

The minimum values of Sa_{O_2} and FE'_{O_2} and the duration of any reduction in Sa_{O_2} below baseline values were obtained from the records for each of the 15-min periods following gas administrations.

No attempt was made to influence the subject's breathing pattern unless Sa_{O_2} decreased to < 80%, when the subject was instructed to take a deep breath.

Data were analysed by the Wilcoxon signed rank test.

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TABLE I. *Minimum Sa_{O_2} and FE'_{O_2} (mean (SD)) and duration of depression of Sa_{O_2} below baseline following each respiratory manoeuvre.* *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ *for comparisons of nitrous oxide in oxygen with the other mixtures (Wilcoxon signed rank test)*

Ventilatory pattern	Gas mixture	Minimum Sa_{O_2} (%)	Minimum FE'_{O_2} (%)	Time less than baseline Sa_{O_2} (s)
Hyper-ventilation	79% N_2/O_2	90.1 (4.4)	12.5 (1.7)	285 (154)
	50% N_2/O_2	93.0 (2.8)	12.8 (1.5)	254 (156)
	50% N_2O/O_2	85.6 (7.6)*	10.4 (1.2)**	501 (176)***
Normal	79% N_2/O_2	97.2 (1.2)	13.8 (0.9)	0
	50% N_2/O_2	96.4 (1.3)	14.6 (0.6)	0
	50% N_2O/O_2	94.0 (2.0)**	12.2 (1.7)*	415 (141)**

Baseline Sa_{O_2} and FE'_{O_2} were 96.8 (1.3)% and 15.7 (0.7)%, respectively (table I). There were small but clinically unimportant decreases in Sa_{O_2} and FE'_{O_2} after 50% nitrous oxide in oxygen with normal ventilation compared with the other mixtures. After hyperventilation, Sa_{O_2} and FE'_{O_2} were depressed for all gas mixtures, but they were depressed most, in both magnitude and duration, following 50% nitrous oxide in oxygen.

COMMENT

It is established that a period of hypoxaemia may occur during air breathing after the administration of 70–80% nitrous oxide in oxygen [1], but it has not been reported after 50% nitrous oxide in oxygen. Indeed, it has been suggested that, during labour, maternal Pa_{O_2} is not worsened by administration of Entonox [3].

Hypoxaemia is known to occur after hyperventilation [4] because of reduced ventilatory drive caused by hypocapnia. Thus the reductions in Sa_{O_2} and FE'_{O_2} seen in this study after hyperventilation were anticipated. However, there was a much greater reduction in Sa_{O_2} after hyperventilation with 50% nitrous oxide in oxygen than with the other mixtures. This suggests that the nitrous oxide had an effect additional to that of hyperventilation alone. The mechanism of this phenomenon is not clear, but it might result from: an effect of nitrous oxide on ventilatory drive; the ventilatory response to hypoxia; $\dot{V}/\dot{Q}$ mismatch; or diffusion hypoxia.

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Br. J. Anaesth. (1989), **63**, 348–350

NEUROMUSCULAR BLOCK BY SUXAMETHONIUM FOLLOWING TREATMENT WITH HISTAMINE TYPE 2 ANTAGONISTS OR METOCLOPRAMIDE

D. R. TURNER, Y. J. KAO AND C. BIVONA

SUMMARY

We have examined the effect of preoperative i.v. administration of three different histamine type 2 (H_2) antagonists (cimetidine 400 mg, ranitidine 80 mg and famotidine 20 mg) or metoclopramide 10 mg i.v. on the duration of neuromuscular block produced by an intubating dose (1 mg kg^{-1}) of suxamethonium. The study was conducted blindly in 70 post partum patients, weighing between 45 and 120 kg, scheduled for tubal ligation. The duration of neuromuscular block following suxamethonium was measured from a chart recording of train-of-four (TOF) electromyographic responses. The time from onset of 95% block to 25% recovery ("block time") was not significantly different between the groups receiving cimetidine (A), ranitidine (B), famotidine (C), and control (E). However, there was prolongation of neuromuscular block in patients receiving suxamethonium and metoclopramide (D).

Aspiration of stomach contents in the perioperative period remains a major cause of anaesthetic morbidity in the pregnant patient [1]. It is common practice to administer antacids to patients at risk. In some centres, type 2 histamine (H_2) antagonists are given routinely in an effort to reduce gastric volumes or acidity, or both. Hodgkinson and colleagues [2] demonstrated that a combination of oral cimetidine the night before surgery and an i.m. dose 1–3 h before induction of anaesthesia ensured a gastric pH greater than 2.5 at induction for Caesarean section. Gwee and Cheah [3] stressed that drug interactions might occur as a result of the anticholinesterase, ganglion blocking and neuromuscular blocking properties of cimetidine and ranitidine. Kambam, Dymond and Krestow [4] reported that pretreatment of non-pregnant patients with cimetidine 300 mg orally the night before and 2 h before operation led to a prolongation of block by a factor of at least 2. Therefore, prolongation of neuromuscular block by H_2 antagonists might become clinically more significant in pregnant patients, who have lower than normal concentrations of pseudocholinesterase.

Metoclopramide promotes anterograde peristalsis in the gastrointestinal tract and has been used extensively in the preanaesthetic period for prevention of gastric regurgitation. It was included in this study because it can prevent postoperative nausea and vomiting and this property was considered desirable in the puerperal patient.

We conducted a randomized controlled clinical trial to see if prolongation of block occurred with the H_2 antagonists and metoclopramide in puerperal patients and if the effect was clinically important.

METHODS AND RESULTS

Written informed consent was obtained from all patients and the study was approved by the local Institutional Review Board.

Seventy ASA grade I or II patients weighing between 45 and 120 kg and scheduled for post partum tubal ligation surgery were allocated

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TABLE I. *Time to 25% recovery (min) for patients in each group, illustrating individual patient variation within the groups.* **P < 0.05 compared with control*

Patient	Control	Metoclopramide	Ranitidine	Cimetidine	Famotidine
1	9.4	10.0	6.3	8.5	6.5
2	9.2	9.0	6.1	10.4	8.5
3	6.7	6.9	8.1	8.3	5.2
4	3.7	13.4	10.2	6.5	7.1
5	9.6	9.5	12.1	6.0	7.3
6	6.1	9.4	5.2	7.3	8.1
7	10.6	10.3	6.0	6.3	9.2
8	8.3	12.3	2.9	12.5	7.3
9	9.4	10.2	9.0	4.5	6.7
10	8.5	9.4	6.3	15.6	11.3
11	7.1	7.9			
12	10.0	5.4			
13	9.8	8.3			
14	8.3	11.1			
15	8.1	8.5			
16	6.4	10.8			
17	5.2	16.3			
18	5.0	8.3			
19	7.5	9.8			
20	5.5				
21	13.8				
Mean	8.00	9.83*	7.22	8.59	7.72
SD	2.31	2.40	2.5	3.2	1.6

randomly to five groups. Group A (10 patients) received cimetidine 400 mg; group B (10 patients) ranitidine 80 mg; group C (10 patients) famotidine 20 mg; group D (19 patients) metoclopramide 10 mg; group E (21 patients) served as control. The mean (SD) weights of each group were 69.1 (16.8), 68.5 (11.6), 75.6 (21.9), 74.6 (10.4) and 67.1 (12.1) kg, respectively. The H_2 antagonist agents or metoclopramide were given 1–2 h before induction of anaesthesia with thiopentone 4 mg kg^{-1}. All patients received a balanced nitrous oxide–opioid anaesthetic comprising sufentanil 35–60 μg, hyoscine 0.2 mg and 67% nitrous oxide in oxygen. No volatile agent was used at any time during the study.

Muscle relaxation was provided with an initial dose of suxamethonium 1 mg kg^{-1} i.v. When 95% depression of baseline twitch height was reached, the trachea was intubated. Times from 95% depression of baseline twitch to 25% recovery of activity were measured from a graphic recording obtained with a Datex Neuromuscular Transmission (NMT) Monitor. The ulnar nerve was stimulated at the wrist with four supramaximal stimuli at 2 Hz and this train-of-four (TOF) pattern was repeated every 10 s. A grounding electrode over the median nerve isolated the stimulating current from the sensing electrodes which detected electromyographic (EMG) activity in the adductor pollicis muscle. This electrical signal was integrated, compared with the control signal, and the measured activity was expressed graphically as a percentage of this control. The anaesthetist was unaware of the group to which the patient was allocated.

The block time data were analysed with a one-way analysis of variance and Newman–Keuls multiple range test. A two tailed Student's *t* test was used to evaluate the significance of any difference.

The time to 25% recovery in the metoclopramide group was significantly different from control, ranitidine and famotidine groups (table I). There was a prolongation of block in comparison with control when suxamethonium was preceded by metoclopramide. This difference was significant ($P < 0.05$, two-tailed Student's *t* test).

COMMENT

Serum pseudocholinesterase activity decreases by 30% during pregnancy and remains depressed during the postpartum period. Although sensitivity to suxamethonium might be expected in puerperal patients, this does not appear to occur in clinical practice, probably because of changes in volume of distribution at term [5]. However, administration of another drug which slows the metabolism of suxamethonium and potentiates its action could be clinically important in this group of susceptible patients.

The use of an H_2 antagonist for premedication in the pregnant patient has become popular in recent years and, although it is known that these drugs may inhibit plasma pseudocholinesterase activity [3], we were unable to demonstrate any prolongation of suxamethonium activity in the puerperal patients who received an H_2 antagonist. On the other hand, Kambam, Dymond and Krestow reported prolongation of the action of suxamethonium 1.5 mg kg^{-1} by a factor of 2–2.5 after cimetidine [4]. The difference in patient population and schedule of administration of cimetidine and suxamethonium may account for this discrepancy.

Metoclopramide 10 mg i.v. was the only drug tested which prolonged the action of suxamethonium (by 25 %). The potent antipseudocholinesterase activity of metoclopramide may account for this prolongation [6]. This is not a problem in clinical practice, but it might become significant if larger doses of each drug are used in a rapid sequence induction.

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Br. J. Anaesth. (1989), **63**, 351–353

PREMEDICATION DETERMINES THE CIRCULATORY RESPONSES TO RAPID SEQUENCE INDUCTION WITH SUFENTANIL FOR CARDIAC SURGERY

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SUMMARY

Thirty-three patients undergoing elective aortocoronary bypass were allocated randomly to receive morphine 0.1 mg kg^{-1} i.m. and either lorazepam 50 μg kg^{-1} by mouth or hyoscine 6 μg kg^{-1} i.m. before rapid sequence induction of anaesthesia with sufentanil 5 μg kg^{-1} i.v. and suxamethonium 1 mg kg^{-1} i.v. Following induction and tracheal intubation, patients premedicated with hyoscine had a significantly higher mean heart rate, mean arterial pressure, cardiac index and left ventricular stroke-work index than patients premedicated with lorazepam. The incidence of new myocardial ischaemia was low in both groups.

Premedicant drugs are often selected to relieve anxiety, produce amnesia or reduce oropharyngeal secretions. Such drugs may influence perioperative haemodynamic state and the extent of myocardial ischaemia, particularly during rapid-sequence induction of anaesthesia. We have compared, therefore, the effects of morphine and lorazepam with those of morphine and hyoscine on haemodynamic responses and the incidence of myocardial ischaemia in patients anaesthetized with a rapid sequence technique using sufentanil and suxamethonium, in patients undergoing aortocoronary bypass grafting. Differences in premedication, if demonstrated for sufentanil–suxamethonium as for fentanyl–atracurium [1], may clarify recent controversies on the choice of opioid and muscle relaxant in patients with severe coronary artery disease [2, 3].

METHODS AND RESULTS

Following approval of the study by the Institutional Review Board and informed patient consent, we performed a randomized, unblinded study in 33 patients undergoing elective aortocoronary bypass grafting. Patients received morphine sulphate 0.1 mg kg^{-1} i.m. and either hyoscine 6 μg kg^{-1} i.m. ($n = 16$) or lorazepam 50 μg kg^{-1} by mouth ($n = 17$) with their usual antianginal medications 90 min before anaesthesia. Exclusion criteria included myocardial infarction within 7 days, left ventricular ejection fraction < 0.5, vasoactive drug infusions, pacemakers, ethanol or drug abuse, or any medical condition which contraindicated the drugs used (e.g. malignant hyperpyrexia susceptibility).

Patients inhaled oxygen-enriched air and were monitored continuously with finger pulse oximetry and electrocardiography (leads II and V5). Electrocardiographic data were recorded continuously during the study for later analysis. I.v., i.a. and pulmonary arterial catheters were inserted. Sufficient volumes of fluids were infused i.v. to increase the pulmonary arterial diastolic pressure to a value exceeding 10 mm Hg.

For rapid sequence induction of anaesthesia, sufentanil 5 μg kg^{-1} and suxamethonium 1 mg kg^{-1} were administered i.v. in less than 10 s. We repeated all measurements 1 min after induction and immediately afterwards the trachea was intubated. Laryngoscopy was accomplished easily within 20 s in all patients and was not accompanied by arterial oxygen desaturation. At 3 and 6 min after induction, measurements were repeated.

Hypotension (defined as a decrease in systolic

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TABLE I. *Mean (SD) haemodynamic responses to induction of anaesthesia with sufentanil and suxamethonium following premedication with morphine and either hyoscine* ($n = 16$) *or lorazepam* ($n = 17$). *Intubation of the trachea was performed immediately following the 1-min data collection.* $P < 0.05$ *compared with :* **pre-induction value by paired* t *test;* †*corresponding value of patients receiving the other premedication (analysis of co-variance)*

			After induction		
	Premedication	Before induction	1 min	3 min	6 min
Heart rate (beat min^{-1})	Hyoscine	62 (8)	66 (11)*	73 (10)*†	71 (12)*†
	Lorazepam	63 (12)	63 (14)	62 (14)†	60 (14)†
Mean arterial pressure (mm Hg)	Hyoscine	94 (13)	83 (14)*	92 (19)	92 (16)
	Lorazepam	97 (14)	81 (15)*	82 (15)	86 (13)
Mean pulmonary arterial pressure (mm Hg)	Hyoscine	23 (6)	23 (6)	27 (6)	27 (6)
	Lorazepam	24 (7)	25 (6)	28 (5)	27 (6)
Central venous pressure (mm Hg)	Hyoscine	11 (4)	12 (4)	13 (4)	13 (4)*
	Lorazepam	11 (4)	12 (6)	13 (5)*	14 (5)*
Cardiac index (litre min^{-1} m^{-2})	Hyoscine	2.8 (0.6)	2.9 (0.6)	3.3 (1.0)*†	3.3 (1.0)*†
	Lorazepam	2.7 (0.6)	2.8 (0.7)	2.7 (0.8)†	2.5 (0.8)†
Left ventricular stroke work index (g m m^{-2})	Hyoscine	48 (12)	41 (13)*	47 (15)†	50 (15)†
	Lorazepam	49 (8)	39 (10)*	40 (12)*†	39 (10)*†

arterial pressure to 90 mm Hg or less) was treated with phenylephrine i.v. New (or greater degrees of) ischaemia were treated with nitroglycerin i.v. Combined hypertension and tachycardia were treated initially with increments of sufentanil (up to five additional doses of 1 μg kg^{-1} i.v.) followed, if necessary, by enflurane.

After the study was completed (i.e., following the 6-min measurement), anaesthesia was maintained with sufentanil (all patients received an additional 5 μg kg^{-1} for a total of 10 μg kg^{-1}); metocurine, pancuronium, or both; lorazepam 2 mg administered during the rewarming phase of cardiopulmonary bypass; and (in most subjects) enflurane. After operation, 30 of the 33 patients were assessed using a 12-lead electrocardiograph. Myocardial ischaemia during and after operation was assessed as an ST segment depression of $\geqslant 1$ mm, measured 80 ms following the J point. All preoperative, intraoperative and postoperative electrocardiograms were reviewed by a cardiologist (R.L.R.) who was unaware of the patients' premedication.

Numerical data were found to be distributed normally and were analysed statistically by analysis of variance for repeated measures (ANOVA), analysis of covariance (ANOCOVA), or Student's *t* test. We used Fisher's exact test or Chi-square to compare baseline demographic data.

Patients in each group were similar with respect to weight and left ventricular ejection fraction. There were no differences between groups in the numbers of patients receiving beta-blockers or calcium channel blockers, or in the number of patients who had previously suffered a myocardial infarction. Preinduction haemodynamic data following the two schemes of premedication were also similar (table I). After induction of anaesthesia, there was a significant difference between groups (ANOVA) in heart rate ($P < 0.01$), mean arterial pressure ($P = 0.03$) and cardiac index ($P = 0.02$).

Consistent alterations associated with both premedication and induction of anaesthesia were detected by ANOVA for cardiac index ($P = 0.004$) and left ventricular stroke-work index ($P = 0.0517$). Intergroup comparisons by ANOCOVA (for those variables influenced consistently by induction of anaesthesia) are indicated in table I. There were significant differences at 6 min for heart rate, cardiac index and left ventricular stroke-work index.

Following induction of anaesthesia, five patients required drug interventions. Hypotension was corrected in three patients: two had received lorazepam and one had received hyoscine. Three patients, all of whom were premedicated with hyoscine, required additional sufentanil to correct hypertension and tachycardia. Before induction of anaesthesia, seven patients (three hyoscine, four lorazepam) showed electrocardiographic evidence of myocardial ischaemia. Five improved following induction and tracheal intubation (three hyoscine, two lorazepam), and two worsened (both lorazepam). No patient developed new ischaemia during the study period.

None of the 30 patients evaluated 1 or more days after operation (15 hyoscine, 15 lorazepam) demonstrated evidence of perioperative myocardial infarction. None of the patients reported awareness during surgery.

COMMENT

Our data show that sedative premedication influenced haemodynamic variables after rapid sequence induction with sufentanil and suxamethonium. Although haemodynamic values were similar before induction after either premedication, after induction and tracheal intubation, patients premedicated with morphine and hyoscine had significantly higher heart rates and cardiac and left ventricular stroke-work indices than the group receiving morphine and lorazepam. We attribute these haemodynamic differences to mild circulatory depression caused by interaction between lorazepam and sufentanil.

During fentanyl–atracurium anaesthesia, Thomson and colleagues [1] observed that patients premedicated with oral lorazepam had haemodynamic values that differed from those following premedication with i.m. morphine–hyoscine. They speculated that premedication may influence haemodynamic responses after different opioid–relaxant combinations. This may explain why Thomson and Putnins [2] found that fentanyl–pancuronium was associated with an unacceptably high incidence of tachycardia, hypertension and myocardial ischaemia in patients premedicated with morphine–hyoscine, whereas Gravlee and colleagues [3] found that this was the optimum combination following premedication with morphine–lorazepam.

We had expected that bradycardia would occur frequently with our technique [4,5]. No bradycardia required treatment, although the lorazepam-premedicated patients maintained significantly lower heart rates than those who received hyoscine. Moreover, we often observed that sudden bradycardia induced by sufentanil was apparently reversed coincidentally with suxamethonium fasciculations. This is consistent with the study observations of Royster and colleagues [6], who observed that tachycardia occurred when suxamethonium was administered to dogs anaesthetized with large doses of fentanyl.

In summary, either lorazepam or hyoscine, when combined with morphine, provided effective premedication for rapid sequence induction of anaesthesia with sufentanil and suxamethonium. The incidence of adverse haemodynamic changes and of myocardial ischaemia was very small. However, our data also suggest that the type of premedication may influence circulatory responses to induction of anaesthesia. In some patients, the greater heart rate and cardiac index after hyoscine compared with lorazepam premedication may increase the risk of ischaemia.

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Br. J. Anaesth. (1989), **63**, 354–356

COMPARISON OF PIROXICAM WITH PLACEBO IN THE MANAGEMENT OF PAIN AFTER TOTAL HIP REPLACEMENT

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SUMMARY

A randomized double-blind controlled study was undertaken to assess the analgesic efficacy of piroxicam. Twenty-four patients underwent total hip replacement under spinal anaesthetic; after operation, they received a 3-day course of either placebo ($n = 12$) or piroxicam ($n = 12$). Adequate analgesia was provided for 48 h by a patient-controlled analgesia system delivering morphine. Patients receiving piroxicam required 50% less morphine than the control group (38 mg compared with 76 mg ($P < 0.002$)). This technique was tolerated well and there were no significant side effects.

Postoperative pain is difficult to treat effectively, as suggested by the many techniques available. Non-steroidal anti-inflammatory drugs (NSAID) may be effective in the control of postoperative pain [1, 2] and they may be used to reduce opioid requirements and, hence, side effects [3, 4].

We have investigated the efficacy of piroxicam as an adjunct to opioid analgesics for pain relief after total hip replacement in a randomized, prospective, double-blind study.

METHODS AND RESULTS

We studied patients of ASA grade I or II, aged 18–85 yr, undergoing elective total hip replacement under spinal anaesthesia. Patients were excluded if piroxicam was contraindicated because of coagulopathy, history of peptic ulceration, hypersensitivity to NSAID or aspirin, or the concomitant administration of steroids or lithium. Patients were excluded also if they had been receiving other NSAID in the previous 2 days or piroxicam within 5 days before surgery. Analgesia was provided by means of paracetamol in the 24 h before surgery.

The study was approved by the hospital Ethics Committee. Patients were allocated randomly to receive either capsules of piroxicam (20 mg each), or placebo at designated times. Two capsules were given at 22:00 on the evening before operation, two capsules on the evening of the day of surgery and one capsule on the evening of the first day after operation.

A full explanation of the On-Demand Analgesic Computer (ODAC, Janssen Scientific Instruments, Beerse, Belgium) was given and informed consent obtained.

The anaesthetic technique was standardized and comprised temazepam premedication 0.3 mg kg^{-1} to the nearest 10 mg orally 1 h before operation. All patients underwent spinal anaesthesia with 0.75% bupivacaine 2.75–3.25 ml; no supplementary analgesia was administered. Perioperative oxygen therapy was administered and sedation provided with midazolam 1–2 mg i.v. as required.

The ODAC was attached soon after the patient's return to the ward and analgesic requirements were recorded by means of a printer. The ODAC was set to deliver morphine in 2-mg i.v. boluses to a maximum of 4 mg h^{-1} with a lockout interval of 9 min. If pain relief was inadequate, morphine 10 mg i.m. or paracetamol 1 g orally was administered.

Patients were assessed 4 h after injection of bupivacaine to ensure that the level of block was below the 10th thoracic dermatome. Any adverse

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effects were noted at 24 and 48 h after surgery. Postoperative pain was assessed at 48 h using a seven-point visual scale (0 = no pain; 6 = "worst pain imaginable").

After completion of the trial, the randomization code was broken and data analysed using Student's t test, Chi-squared test with Yates' correction or two-tailed Wilcoxon test as appropriate.

Thirty-seven patients entered the trial, but 13 were withdrawn: four patients required general anaesthesia because of unsuccessful spinal block; six did not receive the capsules according to the procedure; one patient received an extradural block; one required ketamine towards the end of a long procedure (255 min) to supplement a receding spinal block. One patient in the piroxicam group with mild untreated Parkinson's disease was unable to take the capsules or operate the ODAC after operation. This was not thought to be related to the piroxicam, as he had a similar episode the previous year following premedication with temazepam. Table I summarizes the data.

COMMENT

Patients in the piroxicam group required 50% less morphine than the control group in the 48-h postoperative period ($P < 0.002$). Use of the ODAC system provided a good indication of the magnitude of pain. The demand rate probably reflects a balance between the attainment of desirable analgesia and avoidance of undesirable effects. This is supported by the similar mean pain scores and incidence of nausea and vomiting in both groups. When present, vomiting occurred shortly after return to the ward and on no occasion did it interfere with the oral administration of piroxicam. Although the ODAC was programmed to deliver a maximum of morphine of only 4 mg h^{-1}, this satisfied most patients, as the amount of additional opioid given i.m. was low in both groups.

Other studies [3, 5] have shown a reduction in opioid consumption of 20–30% after the use of NSAID as adjuncts to analgesia after abdominal surgery. Patients undergoing hip replacement are immobile for prolonged periods both during surgery and in bed after operation. This often produces discomfort in the shoulders, back and pelvic girdle. Backache is a frequent complaint, aggravated by the loss of lumbar muscle tone during spinal anaesthesia. This musculoskeletal discomfort may be a major determinant of opioid requirement.

More serious side effects produced by opioids include respiratory depression. In the Sleep Apnoea Syndrome, apnoeic episodes and oxygen desaturation occur during Rapid Eye Movement (REM) sleep. Morphine abolishes REM sleep on

TABLE I. *Comparison of groups (mean (SEM)).* † *S = Short (< 157.5 cm); M = medium (157.5–177.8 cm); T = tall (> 177.8 cm).* ‡ *0 = no pain; 6 = worst pain imaginable.* *P < 0.002

	Control (n = 12)		Piroxicam (n = 12)
Age (yr)	66 (3.7)		69 (2.7)
Female:Male	5:7		9:3
Weight (kg)	74 (3.6)		69 (4.9)
Height (S:M:T)†	1:10:1		5:5:2
Operation time (min)	110 (7.5)		104 (7.5)
Midazolam (mg)	4.3 (0.8)		4.5 (0.5)
Prosthesis (cement:no cement)	9:3		9:3
Total 48-h consumption of opioid (mg)	76 (9.2)	*	38 (4.4)
Morphine i.m. supplements (mg)	9.6 (4.1)		3.5 (1.8)
Morphine delivered by ODAC (mg)	66.4 (6.5)	*	34.5 (4.2)
Pain score (0–6)‡	2.6 (0.4)		2 (0.4)
Nausea (No. of patients)	7		5
Vomiting (No. of patients)	5		4
Blood loss (ml) (n = 6)	888 (123)		918 (167)

the night immediately after surgery, which leads to a "catching up" period on subsequent nights, during which there is prolonged REM sleep with an increased tendency to sleep apnoea. Morphine also induces apnoea in the absence of REM sleep. Analgesic techniques which avoid the use of opioids reduce these episodes of apnoea [6].

NSAID predispose to gastrointestinal haemorrhage and perforation with an incidence of about one in 6000 prescriptions. The dose and duration of NSAID treatment are the most important determinants of mucosal damage, and we can find no reports of these complications occuring during a short course of treatment. There was no evidence of gastrointestinal irritation in our patients, but we excluded those with a history of dyspepsia.

In other studies [2–5] there was only one [4] report of a possible increase in wound haemorrhage after treatment with NSAID. In those patients who did have blood loss measured, the extent of haemorrhage was similar in both groups, but further studies are needed to evaluate this potential complication. We chose piroxicam because its analgesic and anti-inflammatory properties are well documented. It has a half-life exceeding 30 h which is unique among NSAID and permits dosage once per day, and therefore better compliance.

ACKNOWLEDGEMENT

We are grateful to Pfizer Ltd for providing the piroxicam/placebo capsules and ODAC machines.

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Br. J. Anaesth. (1989), **63**, 357–359

SOMATOSENSORY-EVOKED POTENTIALS DURING BLOCK OF SURGICAL STIMULATION WITH PROPOFOL

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SUMMARY

The effect of propofol on somatosensory evoked potentials was assessed during different intraoperative stimuli in prolonged (> 2 h) abdominal operations. SSEP were used to evaluate the extent of block of sensory nerve conduction at the following stages: preinduction; during steady state anaesthesia; during traction of the mesentery; 10 min after anaesthesia. Propofol 100 μg kg^{-1} min^{-1} and nitrous oxide in oxygen anaesthesia induced a significant decrease in amplitude of the SSEP; noxious stimulation resulted in an increase in afferent nerve transmission and a concomitant increase of amplitude of the late evoked potential. After operation, impulse transmission recovered rapidly and the amplitude was similar to control at 10 min after anaesthesia.

It has been suggested that evoked potentials may be used to assess depth of analgesia/anaesthesia [1, 2]. The late SSEP (> 50 ms) show close correlation with individual pain perception after the administration of centrally acting analgesics [3, 4]. We have evaluated the extent of afferent nociceptive input to higher cortical structures during various stages of prolonged (> 2 h) anaesthesia with nitrous oxide in oxygen plus propofol.

METHODS AND RESULTS

After obtaining informed written consent, we studied 15 patients (mean age 60 yr, mean weight 63 kg) undergoing elective abdominal surgery. Premedication comprised pethidine 0.5 mg kg^{-1}, promethazine 1.0 mg kg^{-1} and atropine 0.01 mg kg^{-1} i.m, 45 min before anaesthesia. Anaesthesia was induced with propofol 2 mg kg^{-1} i.v. followed by suxamethonium 1.0 mg kg^{-1} to facilitate tracheal intubation; maintenance consisted of an infusion of propofol 100 μg kg^{-1} min (6 mg kg^{-1} h^{-1}) and 66% nitrous oxide in oxygen. Pancuronium was used to maintain neuromuscular block and ventilation was controlled to maintain normocapnia. Core temperature was measured by a probe in the oesophagus to verify that there was no decrease below 36 °C.

Ten minutes before the end of anaesthesia, the propofol infusion was discontinued and the lungs ventilated with 100% oxygen.

For measurement of evoked potential from the right or left median nerve, silver–silver chloride cup-electrodes were placed at $C_{3'}$-FpZ or $C_{4'}$-FpZ, respectively (EEG 10/20 system). The ground electrode was placed around the right or left arm. Impedance was maintained less than 2 KΩ at all times, by cleaning and abrading the skin at the site of application, the use of freshly chlorided silver–silver chloride cup-electrodes and application of sufficient electrode gel into the dome of the electrode.

The median nerve was stimulated at the wrist with a rectangular pulse of 5 Hz, 0.2 ms duration and a constant current 1 mA above motor threshold (Digi Stim II, Neuro Technology, Houston) using conventional ECG pregelled stick-on electrodes. Two hundred and fifty-six impulses were amplified, filtered (30–15000 Hz) and averaged with a Lifescan EEG monitor (Neurometrics, San Diego) using a sampling rate of 3.1 KHz.

After base-line preinduction values were recorded and replicated, median nerve evoked

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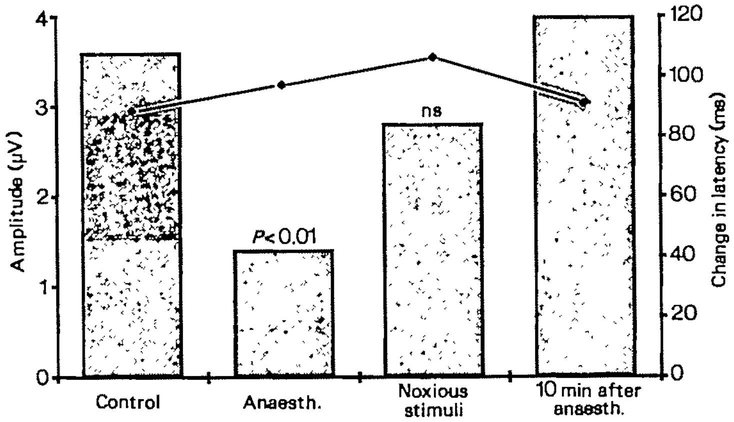

FIG. 1. Mean amplitude height (stippled columns) and latency change of the N_{100} peak (——) of somatosensory evoked potentials at different episodes. Significance compared with control.

potentials were recorded repetitively. The following episodes were compared: before induction (control); during steady state anaesthesia; during traction of the mesentery; and 10 min after anaesthesia.

The major negative deflection of the late evoked potential wave (N_{100}) was analysed in terms of peak to base amplitude (μV) and latency (ms) changes.

Data were analysed statistically by Friedman's rank analysis of variance followed by pairwise comparison of Wilcoxon and Wilcox. Significance was defined as $P < 0.05$.

Cortical responses during anaesthesia were depressed markedly as there was a significant ($P < 0.01$) decrease in amplitude height from a mean (SD) of 3.6 (2.7) to 1.4 (0.8) μV (fig. 1). Traction of the mesentry resulted in a significant increase in amplitude compared with steady state anaesthesia ($P > 0.05$) with a mean of 2.8 (1.1) μV and little change in latency. This increase was not significant in comparison with the amplitude height of the preoperative control period (fig. 1).

Ten minutes after the end of anaesthesia, there was a return of amplitude of evoked potential towards control (4.0 (2.5) μV) (fig. 1).

COMMENT

Our results demonstrate the effects of propofol–nitrous oxide in oxygen anaesthesia on SSEP signals, and the benefit of using the amplitude of the evoked potential to indicate reduction in depth of anaesthesia during the course of anaesthesia. Increase in amplitude during traction of the mesentery resulted from generalized CNS activation (arousal). Activation offsets the effects of anaesthesia/analgesia, and is followed by an increase in nerve traffic reaching higher cortical centres. As an increase in noxious stimulation increases the amount of afferent nerve potentials from the median nerve, the evoked peaks result in an increase in amplitude height at the cortical site. Thus evoked potentials demonstrate insufficient anaesthesia/analgesia.

The use of evoked potentials as a guide to depth of anaesthesia has been advocated by Sebel [1, 2] and others [4, 5]. Our data obtained 10 min after anaesthesia confirm this view. At this stage, amplitude height of the SSEP reached pre-anaesthetic values, at a time when the anaesthetic action was terminating.

The present data also demonstrate the potential benefit of propofol for prolonged (> 2 h) use. SSEP of patients after propofol reflected fast recovery of nervous conduction and little or no residual depressant effect in the immediate postoperative period. This recovery coincided with the time when patients became co-operative and orientated in time and space, in contrast to enflurane anaesthesia [6].

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PACEMAKER-INDUCED TACHYCARDIA DURING GENERAL ANAESTHESIA: A CASE REPORT

G. M. MADSEN AND C. ANDERSEN

SUMMARY

Pacemakers with a rate-responsive function, based on calculation of ventilatory minute volume, may induce tachycardia in patients who undergo hyperventilation during general anaesthesia. If hyperventilation is desired, it is recommended that the pacemaker is reprogrammed in order to avoid tachycardia. If the programming device is not available, a magnet may be placed over the pacemaker site to convert it to fixed-rate pacing.

During recent years, rate-responsive pacemakers have been introduced in order to improve the patient's circulatory adjustment to situations of stress. The common feature in these pacemakers is an increase in pacing rate in response to an increased demand such as exercise.

In rate-responsive pacemakers, various physiological variables (e.g. rate of ventilation, muscle movement, QT interval, temperature, oxygen saturation or pH in mixed venous blood) are used to adjust pacing rate [1]. However, these may demonstrate unexpected episodes of malfunction in uncommon situations (e.g. general anaesthesia) [2, 3]. In this case report we describe the untoward function of a new type of rate-responsive pacemaker (META MV 1202, Telectronics) caused by inadequate knowledge of its mode of action.

CASE HISTORY

A 76-year-old man was admitted to hospital for transurethral resection of the prostate. One month earlier, he had suffered from syncopes. ECG showed complete heart block (3° AV block) with a heart rate of 30 beat min^{-1}. He had no previous cardiopulmonary complaints and was not receiving medication. He was in good physical condition, and a rate-responsive pacemaker was implanted to treat the slow heart rate.

The pacemaker was set to pace at 70–115 beat min^{-1}. Within this interval, the pacing rate depended on the pulmonary ventilation, which was calculated by measurement of changes in thoracic impedance using a low energy pulse (1 mA for 15 µs at 20 Hz) between the pacing electrode and the pulse generator. Transthoracic impedance increases with inspiration and decreases with expiration; the amplitude reflects tidal volume. Changes in tidal volume or rate of ventilation which cause a change in ventilatory minute ventilation induce changes in pacing rate [4].

At the first follow-up after the implantation, the patient performed a bicycle ergometer test. At rest, pacing rate was 70 beat min^{-1} and rate of ventilation was 12 b.p.m. At maximal exercise (80 W) the pacing rate was 115 beat min^{-1} and the rate of ventilation had increased to 22 b.p.m.

At preoperative physical examination, ECG demonstrated 100% pacing at 70 beat min^{-1}. Serum electrolyte and haemoglobin concentrations were within normal limits. The patient was premedicated with diazepam 10 mg orally 4 h before general anaesthesia. Arterial pressure was 140/95 mm Hg. No particular test or investigation of the pacemaker was performed before the operation.

Anaesthesia was induced with midazolam 2.5 mg and thiopentone 200 mg i.v. After a supplement of midazolam 2.5 mg and fentanyl 0.15 mg i.v., neuromuscular block was achieved with gallamine 20 mg and suxamethonium 100 mg to facilitate tracheal intubation. Assisted manual ventilation of the lungs was given

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Accepted for Publication: December 23, 1988.

with 50% nitrous oxide in oxygen 6 litre min^{-1}, via a modified Mapleson D system (Hafnia D). A few minutes after intubation, an increase was noted in the paced heart rate (Diascope, S&W). The patient showed no clinical signs of inadequate anaesthesia, but the paced heart rate continued to increase to 115 beat min^{-1}, so repeated doses of fentanyl and thiopentone were given. Arterial pressure declined from 170/110 mm Hg immediately after intubation, to 90/50 mm Hg at the maximal heart rate of 115 beat min^{-1} 35 min after tracheal intubation. There was no accurate measurement of blood loss, but it was thought to be insignificant. However, because of the progressive hypotension, one unit of blood was given. The manual ventilation was reduced incidentally, and there was a slowing of paced heart rate from 110 to 70 beat min^{-1}.

During the remainder of surgery, heart rate was 70 beat min^{-1}, arterial pressure increased steadily from 95/50 mm Hg to 120/70 mm Hg, and no further supplements of i.v. anaesthetics were given. The patient recovered slowly, with inadequate spontaneous breathing, but this improved after naloxone 0.2 mg i.v. After operation the patient's cardiopulmonary condition was stable.

DISCUSSION

There have been several reports of malfunction or unexpected modes of action of pacemakers [2, 3]. The increasing number of advanced pacemakers has made this subject more relevant to anaesthetists [5].

In recent years, pacemakers have been developed to adjust the pacing rate according to the patient's level of activity, in order to obtain a more physiological response to exercise [6]. During exercise, there is an increase in cardiac output, preload and myocardial contractility [7].

Various activity detecting systems have been developed to create a reliable rate-responsive pacemaker (e.g. by monitoring muscle movement, rate of ventilation, temperature, or the QT interval). During periods of rest, most of the rate-responsive pacemakers pace at a pre-set basic rate, usually because these patients have absent or very slow spontaneous heart rate. At operation, the ECG of these patients displays a regular paced heart rate, and most attention is directed towards pacing failure caused by electrosurgery, which is the most common cause of disturbance [3, 5].

In this case history an unexpected paced tachycardia occurred. This was interpreted as inadequate anaesthesia, and repeated doses of i.v. anaesthetic were given, without effect on the tachycardia. There was a decrease in arterial pressure, caused presumably by increments of thiopentone and fentanyl [8].

The decision to transfuse blood was accompanied by a slowing of the heart rate and a concomitant reduction in manual ventilation associated with the anaesthetist setting up the i.v. infusion.

This case report illustrates the importance of understanding the principles governing the function of a pacemaker. Patients with rate-responsive pacemakers which respond to changes in ventilation should undergo mechanical ventilation during anaesthesia in order to avoid inadvertent hyperventilation. When deliberate hyperventilation is utilized (e.g. in neurosurgery), it is suggested that the pacemaker be reprogrammed to exclude the rate-responsive function. In many situations it may be difficult to obtain access to the programming device and in this case a magnet may be placed over the pacemaker to obtain a temporary reduction in pacing rate. (The META MV 1202 delivers a pacing rate of 99 beat min^{-1}.)

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Br. J. Anaesth. (1989), **63**, 362–364

CLINICAL EVALUATION OF PRESSURE SUPPORT VENTILATION

K. G. STEWART

SUMMARY

A 5-year-old child required a prolonged period of ventilatory assistance, provided in the form of pressure support ventilation. There was a significant negative correlation between the level of pressure support and the Pa_{CO_2}. *Requirements for sedation were reduced with pressure support compared with conventional controlled ventilation. Changing the ventilator trigger level from* -1 *cm* H_2O *to* -3 *cm* H_2O *did not affect* Pa_{CO_2}. *Satisfactory arterial blood-gas tensions were obtained only when the inspiratory pressure was increased to 10 cm* H_2O *above positive end-expiratory pressure.*

Despite the frequent use of pressure support ventilation in patients requiring ventilatory assistance in the intensive care unit, there are few published reports which either confirm clinical benefits from the technique, or suggest the most appropriate machine settings for use. This case report describes a patient who required a prolonged period of ventilatory assistance which was provided in the form of pressure support with no added mandatory ventilator breaths.

CASE REPORT

A 5-yr-old boy (weight 15 kg) underwent cardiac surgery for closure of bilateral modified Blalock Taussig shunts, patch closure of a ventricular septal defect, and right ventricular outflow tract reconstruction using a pericardial gusset. After operation, he required moderate doses of inotropic drugs to control right ventricular failure, underwent a brief period of peritoneal dialysis because of renal impairment, and developed a chest infection. These problems had resolved largely by the 20th day after operation and inotropic support was withdrawn. However, it proved impossible to wean the patient from ventilator support. The surgical repair and cardiac function was judged to be satisfactory by echocardiography, and there was no obvious biochemical reason for the residual respiratory impairment. He was receiving adequate enteral nutrition via a nasogastric tube, and had not received recently any drug likely to cause weakness of ventilatory muscles. A clinical diagnosis of bilateral phrenic nerve palsy was confirmed by ultrasonic diaphragmatic screening.

By day 29 the patient had been weaned to pressure support alone, delivered by a Siemens Elema Servo 900-C ventilator with a humidifying chamber (Fisher and Paykel) placed in the inspiratory limb of the patient tubing. Over the course of the next 26 days his condition remained stable and it was possible to assess the effects of various ventilator settings.

For the main part, the inspiratory pressure was set at 10 cm H_2O greater than positive end-expiratory pressure (PEEP). However, in order to ascertain if further weaning was likely to be successful, each day the pressure support was reduced for varying periods of time. Initially, inspiratory pressure was reduced to 5 cm H_2O on each occasion but, after 5 days, it was decided to reduce the level randomly to any one of five lower settings.

One hundred and four samples were sent for arterial blood-gas analysis during the period of study at the ventilator settings shown in figure 1. All samples were drawn from a radial artery cannula at least 1 h after the most recent adjustment of settings. Thirty-one samples were taken whilst the trigger level (the degree of negative pressure which the patient must generate to activate the inspiratory support of the ven-

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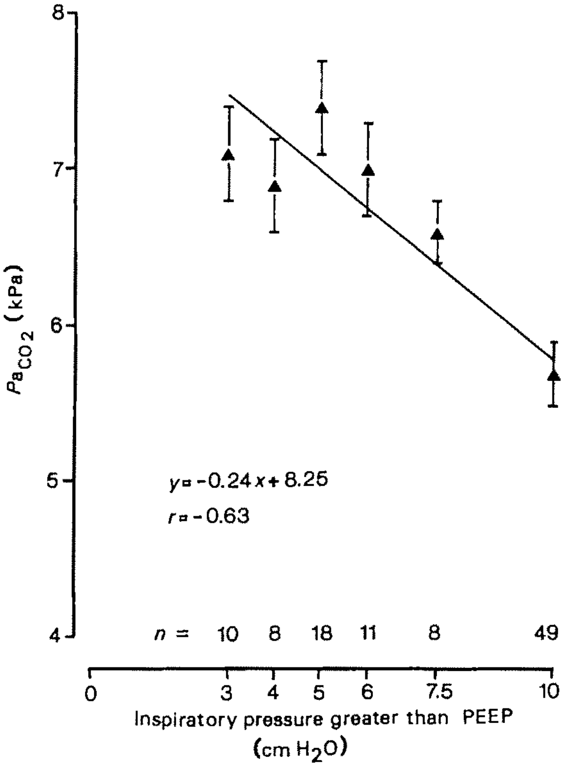

FIG. 1. Relationship between level of pressure support (greater than PEEP) and Pa_{CO_2} (mean, SEM).

tilator) was set at -3 cm H_2O. For the remainder, the trigger was set at -1 cm H_2O. The PEEP control was set at 3 cm H_2O throughout the period of study.

There was a significant negative correlation ($r = -0.63$, $P < 0.001$) between the level of pressure support and the Pa_{CO_2} (fig. 1).

On two occasions, attempts were made to wean the patient to 3 cm H_2O continuous positive airway pressure (CPAP) without pressure support, via a high fresh gas flow T-piece, but his clinical condition deteriorated in less than 1 h, necessitating reintroduction of pressure support. On one of these occasions arterial blood-gas analysis was performed and Pa_{CO_2} was 8.9 kPa.

The trigger level did not affect Pa_{CO_2}. At a trigger of -3 cm H_2O, mean (SD) Pa_{CO_2} was 6.36 (1.07) kPa, compared with 6.47 (1.02) kPa when the setting was -1 cm H_2O.

Cardiovascular measurements remained stable throughout the study period. Systolic arterial pressure and heart rate was unaffected by the level of pressure support. There was no further evidence of renal insufficiency.

Sedation was administered as judged necessary by the nurses attending the patient. Requirements were reduced on pressure support compared with conventional controlled ventilation. Before institution of pressure support, the patient had been receiving a low dose morphine infusion (25 μg kg^{-1} h^{-1}) and he received a mean of 5.0 supplementary doses of sedatives (midazolam or chloral hydrate) per day. On pressure support, the morphine was discontinued and only chloral hydrate (450 mg via nasogastric tube) was given, in a mean of 2.4 doses per day.

Towards the end of the period of study, the patient demonstrated clinical improvement in ventilatory function. Weaning to CPAP was possible over the course of the next 5 days, and the trachea was extubated on the 63rd day after operation.

DISCUSSION

Pressure support is a form of assisted ventilation whereby modern, microprocessor controlled ventilators augment the inspiratory effort of a spontaneously breathing patient. In response to a patient-initiated breath, the machine increases the airway pressure (*P*aw) to a constant, pre-set value. During the expiratory phase, *P*aw decreases to the ambient or the pre-set PEEP level. Although clinical impressions are favourable [1], there are a limited number of published reports evaluating the technique of pressure support. This is partly because of difficulties in obtaining comparable groups of patients in whom controlled studies may be performed. Consequently, most appraisals of pressure support, and of demand valve breathing systems in general, have involved either the study of healthy young adults or the use of simulated models of spontaneous ventilation.

The major disadvantage of demand valve breathing systems is that the negative pressure which the patient must generate to overcome the apparatus inertia and activate the valve may result in an increased work of breathing, as demonstrated by normal subjects breathing through various CPAP delivery systems [2]. Using a model of spontaneous ventilation, a nett reduction in work of breathing was demonstrated when pressure support of 5 cm H_2O or greater was provided from a Servo 900-C ventilator [3]. In models of spontaneous breathing, any decrease in *P*aw during inspiration is interpreted as increased work of breathing, and this is quantified by analysis of the pressure–volume loop. This may be an underestimate of the increased energy utilization during the short period of airway obstruction, where *P*aw may decrease greatly, before the demand valve opens and air flow begins. Katz, Kraemer and Gjerde suggested that this extra work of breathing in patients with impaired respiratory function may result in patient distress which cannot be quantified using lung models [4]. For this reason, it is necessary to assess the clinical effects of different ventilator settings in patients with compromised ventilatory mechanics. Rutten and Bersten, using a lung model which simulated spontaneous adult breathing patterns, concluded that a pressure support setting of at least 10 cm H_2O was needed to obtain clinical benefit [3]. The present study supported their findings, as at lower settings the assistance provided was not sufficient to enable the patient to maintain a satisfactory Pa_{CO_2}.

The CPAP circuit which we used delivered a fresh gas flow of 15 litre min^{-1}, which should have been adequate as this exceeded four times minute volume. However, no reservoir was incorporated in the circuit to act as a capacitance, so it is possible that a reduction in *P*aw did occur at peak inspiratory flow. In a study involving healthy volunteers, Gherini, Peters and Virgilio demonstrated an increased work of breathing with CPAP if *P*aw decreased during inspiration [5], and this may have contributed to the particularly poor results with CPAP in this case. Additionally, it would have been interesting to use greater CPAP as a comparison, although this was not performed.

It was surprising that the trigger level did not affect Pa_{CO_2}. The Servo 900-C has an improved inspiratory valve "stepper motor" compared with its predecessor, allowing the ventilator to respond more rapidly to a patient inspiration. Any additional work of breathing at a trigger setting of -3 cm H_2O must have been insufficiently significant to produce poorer Pa_{CO_2} results.

The question remains unanswered as to whether the use of assisted modes of ventilation may slow the weaning process. In this case, repeated attempts to reduce the pressure support to less than 10 cm H_2O resulted in unsatisfactory Pa_{CO_2} values. However, the use of pressure support, as opposed to controlled ventilation, allowed a reduction in level of sedation and permitted the patient to continue to exercise his other muscles of ventilation, possibly preventing disuse atrophy.

In conclusion, pressure support has been shown to be an effective technique in assisting the spontaneous ventilatory effort of a patient with diaphragmatic paralysis. This clinical study supports the findings of previous laboratory work which suggested that pressures less than 10 cm H_2O greater than baseline are of little benefit. However, controlled clinical studies are required in order to demonstrate any advantage of newer techniques of ventilatory support over the more established methods in terms of eventual outcome.

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Br. J. Anaesth. (1989), **63**, 365–367

CORRESPONDENCE

ARRHYTHMIAS DURING LAPAROSCOPY

Sir,—I was interested to read the study by Burns and colleagues [1] on the effects of nadolol on arrhythmias during laparoscopy performed under general anaesthesia. However, I am disturbed by some of the statements made by the authors.

In the introduction they mention as a cause of arrhythmias increased vagal tone, secondary to peritoneal manipulation, which may lead to severe bradycardia, asystole, or both [2]. Other authors have reported such occurrences [3–6]. At our institution in the past year there have been at least five patients who developed severe bradycardia during laparoscopy. Beta-blockade may increase the incidence of such life-threatening arrhythmias, and may inhibit treatment. Indeed, in the study of Burns and colleagues, the dose of nadolol was decreased to 20 mg, following four cases of profound bradycardia. Carmichael [3] suggested the administration of atropine 0.4–0.6 mg before insufflation of carbon dioxide, to minimize the risk of bradycardia.

The liberal definitions of sinus bradycardia as less than 60 beat min^{-1}, and sinus tachycardia as greater than 100 beat min^{-1}, obscured clinically useful information. It would be more interesting to know the number of patients with a sinus rate of less than (say) 50 beat min^{-1}, or more than 120 beat min^{-1}. It was significant to learn that four of the nadolol-treated group had profound bradycardia requiring treatment with atropine. The only patients in the trial who required intervention were the nadolol-treated group, perhaps itself illustrating clinical significance.

I feel the above discrepancies preclude a recommendation of nadolol to reduce the incidence of arrhythmias during laparoscopy.

P. Myles
Melbourne

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Sir,—Thank you for allowing us to reply to Dr Myles' letter. His group have had five patients with profound bradycardia who required therapy during this type of surgery. We feel that this incidence is high, and may reflect the method of anaesthesia which is used within his institute. Bradycardia may be the result of using a routine policy of artificial ventilation, and the newer neuromuscular blocking agents. We cannot compare our results with his, as we are unaware of the anaesthetic techniques which he used. We feel that the high incidence of arrhythmias noted in our study reflects the effect of halothane anaesthesia. Enflurane may be less arrhythmogenic, and at present we are conducting a study to compare the two agents during laparoscopy.

Dr Myles states that the administration of beta-blocking compounds in this setting may increase the incidence of life-threatening bradyarrhythmias. We have demonstrated that this is not necessarily the case, for example during dental anaesthesia, where the incidence of bradyarrhythmias was significantly reduced following pretreatment with metoprolol [1].

In our present study, four patients were stated to have profound bradycardia—they were pretreated with nadolol 40 mg. None was symptomatic, the procedure was uncomplicated following intraoperative administration of atropine, and there were no sequelae. This point perhaps is not expressed adequately in our paper, and we apologize for this oversight. We agree that the use of atropine for premedication would be a reasonable course of action. In a study to examine the incidence and modification of arrhythmias by therapy, pretreatment with atropine may obscure the true incidence of both sinus bradycardia and sinus tachycardia, hence its avoidance in our study.

In terms of the definition of arrhythmia, any study must have predetermined limits of heart rate, and we believe that those used in the present study are reasonable. It is difficult to see how our range obscures clinically useful information. We have clarified that four patients received atropine, but the bradyarrhythmia was unimportant clinically, and had no sequelae.

We feel that the observations, results and conclusions made under the conditions of this study are appropriate. It is up to each individual anaesthetist to decide whether or not to consider the use of beta-blockers routinely, or to limit their use to patients who may benefit from such premedication.

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D. M. Hart
R. L. Hughes
A. W. Kelman
W. S. Hillis
Glasgow

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UNIVERSAL BREATHING SYSTEM?

Sir,—I was interested to read Bruce and Soni's account of an evaluation of the Enclosed Magill Breathing System [1] and the suggestion that this may be a universal breathing system.

Carden [2] described a modification of the Mapleson A system in 1972 for ventilation in children, and in 1974 for adults [3]. He showed that, provided the total minute ventilation was adequate, the end-tidal carbon dioxide was dependent solely on the fresh gas flow into the system. A ventilator was constructed embodying these ideas, and in 1983 a version of it produced by MIE was bench tested by Fletcher and colleagues [4]. In its "A" mode the breathing system of this ventilator is identical to the more practical of the two Enclosed Mapleson A (EMA) systems described by Miller and Miller [5] in 1988.

Six years experience of using one of these ventilators and approximately 2 years experience with its successor, the Carden Ventmasta (MIE Dentsply), in many hundreds of patients, confirms that these ventilators can indeed ventilate in the Mapleson A mode and that, given adequate total minute volume, end-tidal carbon dioxide is dependent upon the fresh gas inflow and can be controlled very precisely. To maintain an end-tidal carbon dioxide partial pressure of 5 kPa, a fresh gas flow in the range of 50–60 $ml^{-1} min^{-1}$ normally is required. These low flows possibly reflect the decreased production of carbon dioxide in paralysed and well anaesthetized patients undergoing surgery, in comparison with the 100 $ml^{-1} min^{-1}$ required in lightly anaesthetized patients before surgery, described by Bruce and Soni. With the ventilator switched off it is possible to use it for spontaneously breathing patients. The universal breathing system already exists and is available "off the shelf"!

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Nottingham

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COMPLICATIONS OF SPINAL ANAESTHESIA FOLLOWING EXTRADURAL BLOCK FOR CAESAREAN SECTION

Sir,—Drs Stone, Thorburn and Lamb [1] are correct to warn others of the risk of performing intrathecal block in a patient with a recalcitrant extradural block, but their report raises many more questions than it answers. The points I wish to make are inter-related, but for simplicity are considered separately.

The paper states that spinal (i.e. intrathecal) anaesthesia is unpredictable, but it is obvious from the paper, if nothing else [2], that the same may be true of the extradural technique. The sequential or fractional dose extradural technique used in this patient is often used to try to overcome this unpredictability, but occasionally can produce the type of difficulty described. It may lead also to systemic toxicity [3] when repeated injections are used in an attempt to extend an "inadequate" block. The essential problem seems to be that, if there is some obstruction to the spread of local anaesthetic, repeated small injections do not extend beyond that obstruction. Might not a single large (20 ml) injection have done so?

The second question relates to the level of block required for Caesarean section. Why is a block to T10 not adequate? A block to that level would include most if not all the innervation of the birth canal and the lower abdomen. In a motivated patient, a transverse suprapubic incision, a gentle surgeon and judicious supplementation with i.v. or inhaled analgesics (or infiltration with local anaesthetic) could have produced success. Some discomfort might have been present, but not to the extent of delivery "as nature intended"! If a more extensive block was considered essential, why not overcome the obstruction to spread by making a second injection at a higher level [4], or by starting higher in the first place?

My final question relates to the efficacy of treatment of the hypotension that accompanied the eventual extensive intrathecal block. The authors state that hypotension occurred in spite of i.v. ephedrine and fluid loading, but is that so? Certainly, hypotension occurred in spite of fluid loading as 1 litre was administered before any block and more was given thereafter. However, ephedrine was given only *after* the patient became hypotensive and seems to have been much more effective on the few occasions that it was given. Why not use more ephedrine sooner?

J. A. W. Wildsmith
Edinburgh

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Sir,—Thank you for the opportunity to reply to Dr Wildsmith's letter.

A single bolus injection may have avoided the problem of inadequate spread of extradural anaesthesia, but it is standard practice at the Queen Mother's Hospital, Glasgow, as in many centres of obstetric anaesthesia, to use an incremental dose technique. In a hospital where many junior anaesthetists are in training, there are safety aspects which commend the use of such a technique. There is conflicting evidence regarding the plasma concentrations of bupivacaine resulting from differing techniques, but hypotension appears to be more of a problem in the large bolus techniques [1–3].

Dr Wildsmith states that a block to T10 may be adequate for Caesarean section in the motivated patient accepting the undeniable likelihood of some discomfort. However, in our experience, judicious i.v. or inhaled sedation and analgesia would not provide adequate conditions for Caesarean section, and so was not considered to be appropriate. Local infiltration or a second extradural injection may or may not have proved effective, but would have exceeded the manufacturer's recommended dose of bupivacaine and led to an increased risk of toxicity. Although many authors describe the frequent use of doses exceeding that recommended, this should not be done with impunity [4].

Finally, ephedrine was given after the onset of hypotension whilst extradural anaesthesia was being established. With respect to the intrathecal anaesthesia, however, ephedrine was administered i.v. together with the drugs given for induction of general anaesthesia, that is, when the systolic arterial pressure had just been recorded at 95 mm Hg—a minimal degree of hypotension in this patient. The value of the use of prophylactic ephedrine is not clear.

The object of this report was to draw attention to the risks associated with the management of inadequate extradural block, which continues to be a problem in a substantial proportion of patients for Caesarean section. There is no simple, single solution which is applicable to all patients.

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J. Thorburn
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Br. J. Anaesth. (1989), **63**, 368–369

BOOK REVIEWS

Orofacial Pains, 4th Edn. By Welden E. Bell. Published by Year Book Medical Publishers Inc., Chicago. Pp. 448; indexed; illustrated. Price £44.50.

This fourth edition of a book written by a Dental Surgeon for, primarily, dentists is intended as a text for students and a practice manual for health care practitioners. The pages are allocated to three main sections entitled "The Nature of Pain", "Clinical Applications" and "Clinical Pain Syndromes". The first section defines the problems engendered by pain, the involvement of those concerned with treatment and the pathophysiology of pain. The five chapters are verbose, repetitive and sprinkled with inaccuracies, and illustrations are conspicuous by their absence in an area where a clear diagram is worth several pages of text. The second section contains only three chapters and deals with the classification of facial pain, its diagnosis and patient management in a somewhat superficial and confused manner. The text is fragmented, not followed easily and littered liberally with misleading charts or "diagnostic roadmaps" as the author coyly terms them.

Certain statements serve only to underline the dubious conceptual approach of the book—"the objective of analgesics should not be to eliminate pain altogether" being one such. In these chapters there are many errors, both of omission and of commission.

In the third and final section of nine chapters concerned with the presentation and diagnosis of facial pain and the therapeutic options available with which to treat it, the reader is again inundated with a plethora of charts purportedly illustrating classification and clinical information. This proves to be a less than optimum method of presenting data and enhancing the learning process. However, there are many photographic illustrations in this section which are well reproduced, although more lucid labelling would have made them easier both to follow and to relate to the text.

This book cannot be recommended for either the student or graduate dentist, and certainly not for the anaesthetist interested in acute or chronic pain and their control.

K. Budd

Acupuncture, Trigger Points and Musculoskeletal Pain. By P. E. Baldry. Published by Churchill Livingstone, Edinburgh. Pp. 295; indexed; illustrated. Price £27.50.

The title of this readable book reflects its three divisions. Authors writing about acupuncture feel obliged to discuss the historical background. Dr Baldry follows suit, but elegantly. Nineteenth century medicine seemingly was as uncertain of the clinical role as we are now; I liked particularly the 1827 verdict that it was mainly of value in "rheumatism of the fleshy parts".

The dividing line for me between trigger point injection with local anaesthetic and the dry needle acupuncture method described by Dr Baldry is a fine one. We all bemoan the lack of controlled studies of these alternative methods, but they are extremely difficult to study; it is important to admit that many patients appear to benefit, and important, too, to realize that "if no effective treatment exists for a common and distressing condition that runs a fluctuating course, claims will abound for sovereign remedies" [Griffith Edwards, *British Medical Journal*, 1988; **296**: 4]. A major problem with studying alternative methods is provision of adequate controls. It is insufficient in the section on scientific evaluation to state that 35% of us are placebo responders. This is a "single-dose" judgement: repeated challenge with placebo (as in successive menstrual cycles) may show greatly reduced response.

The section on practical application was the one I enjoyed most, covering a variety of painful conditions which are rarely mentioned. Good diagrams showing the extraordinary patterns of pain referral made good clinical common sense to me.

While I remain to be convinced that any difference in outcome could be shown between dry needle acupuncture and local anaesthetic injection to these trigger points, this book may well be of value to those treating painful musculoskeletal conditions.

H. McQuay

Yearbook of Anesthesia 1988. Edited by R. D. Miller, R. R. Kirby, G. W. Ostheimer, M. F. Roizen and R. K. Stoelting. Published by Year Book Medical Publishers, Inc., Chicago, London, Boca Raton. Pp. 368; indexed; illustrated; Price £34.00.

This book consists of abstracts from approximately 100 journals, the literature review being up to Octobef 1987. Some of these journals are familiar to British anaesthetists (for example *British Journal of Anaesthesia* and *Anaesthesia*), some well known but less well read (*Anesthesiology, Annals of Internal Medicine, British Journal of Surgery*) and some probably virtually unknown and unread (*Chinese Medical Journal*). A special virtue of the book, then, is that it culls the non-anaesthetic literature for work which might be of use to anaesthetists. The editors have made some interesting findings in the course of their searches; the whole is a useful warning against parochialism in reading.

There are 14 themes, varying from pharmacology to intraspinal opioids and chronic pain, although the treatment is uneven—the last, for example, earning only one abstract. There is an index and the text contains some well reproduced diagrams and a few illustrations.

The abstracts vary in length, averaging less than one per page. Most, but not all, are followed by editorial comment, again of varying length, from one of the five (American) editors. The shortest, "Amazing!!!!", by Professor Miller, is an apt reaction to a bizarre accident. The longer comments are usually helpful and less patronizing than some have been in the past, although many are critical, for example pointing out methodological errors.

This whole approach does, of course, cause difficulties. The editors have had the advantage of reading the whole text; the reader has only a summary and is unlikely to go back to the original, although it is to be hoped that a book such as this may stimulate further reading. The editor's word is final, and not necessarily better informed than those experts who reviewed the original for publication. In addition the reader, unless he or she be an expert, is unable to put any abstract in the context of previous work; in fact, there is some evidence that the editors themselves are unable to do so, either because they themselves are not conversant with every subject or because they have not sufficient space to expound their views.

The book is eclectic and in no way a systematic review of the literature. It is a miscellany rather than an anthology. It is not a book which many British anaesthetists will buy. It is, however, a book which might be borrowed from the library and dipped into rather than read from cover to cover. There can be few who will not find something of interest and of value in it. In the current vulgarism of the British literati it is a "good read", especially for those with a short attention span. The reviewer enjoyed it.

J. E. Utting

Illustrated Manual of Regional Anaesthesia. By P. Raj, H. Nolte and M. Stanton-Hicks. Published by Springer-Verlag, Berlin, Heidelberg, New York, London, Paris, Tokyo. Pp. 96 (plus 300 transparencies); illustrated. Price DM980.00.

The past few years have seen a considerable increase in the availability of texts on regional anaesthesia. This has been one indicator of the increased interest in this aspect of the specialty, but the number of books available now is such that one has to ask what any new text has to offer that the existing ones do not. This "volume" is at least in an interesting new format and the authors are to be applauded for their enterprise in trying something different. Although its title implies that it is a practical manual, the work is considered better as a brave attempt to present anatomy in the way that anaesthetists view it. Most anatomy texts use a systematic or regional approach and our areas of interest often lie at the boundaries of each section. That is not the case here.

The publication is in two sections. There is a 96-page A4 format text which contains rather brief descriptions of almost all the central and peripheral nerve blocks. Most of the 96 monochrome illustrations in this section are excellent line drawings, but some are clinical photographs which are less clear. The second section comprises 300 colour transparencies in a ring folder. They are in groups of three to six, each corresponding to the text description of a particular block. The idea is that a three-dimensional anatomical picture can be built up by superimposing one on another and the transparencies can be removed from the folder for use as teaching aids. The colours used are a little dull and I did not find that they projected very well, but each sequence of illustrations is well thought out and quite informative.

The authors are from the United States and Germany and the overall tenor reflects not only their origins, but also their very considerable knowledge and experience of regional anaesthesia. Most of the advice given is uncontroversial, although this reviewer was surprised at some of the views expressed, notably that the extent of subarachnoid block is related to the dose of drug injected. It is said that the volume was "...conceived for both the novice and the experienced practitioner..." and I am sure that both could find it useful, but there is one major problem—its almost astronomical price will surely limit its availability, certainly in the U.K. For the equivalent outlay (£300+) one could obtain a copy of each of its major competitors, some of which are little more than 10% of its cost, and collect a very useful library. I understand that it is possible to purchase the work in sections, but this increases the total cost even further. Another problem is that the loose-leaf format of the transparencies will almost certainly result in their loss, especially from library copies used by many readers.

J. A. W. Wildsmith

Disorders of Ventilation, 1st Edn. By J. Shneerson. Published (1988) by Blackwells Scientific Publications, Oxford. Pp. 389; indexed; illustrated. Price £55.00.

It is not often that one encounters a book which fills an obvious gap in the medical literature but *Disorders of Ventilation* is just such a book. As its title implies, it is concerned mainly with disorders which affect the bellows function of the chest wall, as opposed to the gas exchange function of the lungs, and it brings together the cumulative wisdom of several disciplines into one volume which will be of interest to and an education for all those managing patients in respiratory failure.

The book is divided into four parts. The first gives an uncomplicated view of the neural control of breathing, the mechanics of the chest wall and breathing muscles and the influence of sleep on respiration. These chapters set the background for a more detailed analysis of ventilatory failure in the second part, which also includes descriptions of respiratory arrhythmias, sleep apnoea and the physical signs and investigations of these breathing disorders. The third section contains brief descriptions of the medical conditions, neurological, neuromuscular and skeletal, which cause ventilatory failure. The fourth part is the most comprehensive account available of the many methods of treatment of long term respiratory failure. It covers the pharmacological and mechanical, both negative and positive pressure, methods of assisting or augmenting ventilation. Some of the information is of historical interest and many methods of management are likely to be superceded by newer developments such as nasally applied intermittent positive pressure ventilation. Nevertheless, much of interest and practical value is to be found in the description.

The text is clearly written and ideas are expressed in simple terms which do not demand special knowledge. Physiology and clinical significance are linked closely throughout and this is one of the book's strengths. There are helpful flow charts, line diagrams and graphs. The author's own broad practical experience comes through clearly. This volume is a unique distillation of both an extensive study of the literature and a considerable amount of hands-on experience.

The book contains a wealth of knowledge which is particularly well supported by references, and one has the distinct impression that the author is familiar with them all. However, my only criticism of the book is that the 3412 references are placed in alphabetical order in a block at the end of the book, which is a positive disincentive to their examination; it would have been much easier to have scanned the references at the end of each chapter to decide which required follow-up.

Although this book is written primarily for chest physicians, I would recommend it highly to anaesthetists and intensivists.

L. Loh

Talking Health: Conventional and Complementary Approaches. Edited by J. Watt and C. Wood. Published by The Royal Society of Medicine, London. Pp. 167; indexed.

This volume reports the results of a series of colloquia held at the Royal Society of Medicine between 1984 and 1987 under the Chairmanship of Sir James Watt, the then President of the Society. The colloquia resulted from comments made by the Prince of Wales in an address to the British Medical Association in 1983, when he suggested modern medicine would divert our attention from "those ancient, unconscious forces, lying beneath the surface, which still help to shape the psychological attitudes of modern man". The Prince went on to suggest, with the predictable architectural analogy, that "the whole imposing edifice of modern medicine, for all its breathtaking successes is, like the celebrated Tower of Pisa, slightly off balance" and that the balance might be restored by complementary therapies.

There are five main sections. The first, Comparisons and Contrasts, has views from George T. Lewith, Ian McColl and Michael Baum. In the initial colloquia it seems that all the participants were, perhaps, bending over backwards to be patient with one another, because Baum reports feeling like the little boy in the tale of the Emperor's New Clothes. A need for a broader view of health was suggested and some of our pastoral failings were identified. The other sections included Direction for Research, Quality Control in Training and Practice, International Collaboration and finally The Public View from, amongst others, Katherine Whitehorn, who was impressed by the anecdote from Ian McColl. This concerned a family with a desperately sick child, who asked the doctor if he would mind if they took the child to Lourdes. Wishing no disrespect to the doctor's treatment, they nevertheless felt Lourdes might have something to offer. The doctor had the wisdom to say "of course I don't mind; we need all the help we can get".

This is an easy piece of bedtime reading which reminds us of our own shortcomings and those of the complementary practitioners. Perhaps the increased rate of change in biological science and social structure make it more important than ever to take a broad view of the needs of our patients.

M. Clarke

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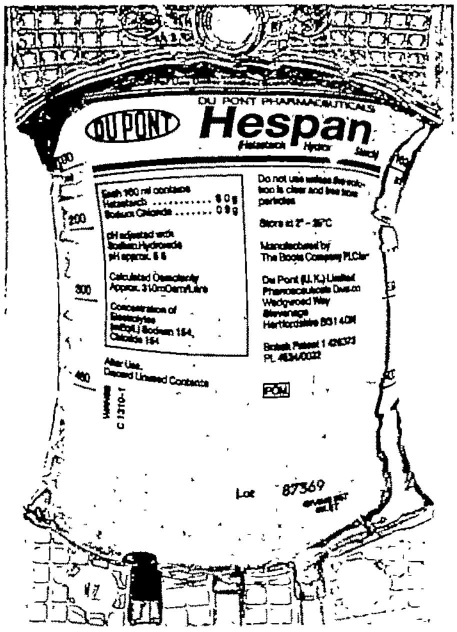

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VOLUME 63, No. 3 *Published monthly* SEPTEMBER 1989

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Trainee rate: U.K./Eire £35.00; Abroad £53.00. Airmail rates on application ISSN 0007-0912

Subscription Department, Professional and Scientific Publications, BMA House, Tavistock Square,
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